EXHIBIT 83

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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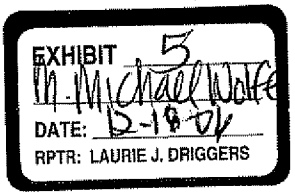
ARTHRITIS ADVISORY COMMITTEE

NDA 20-988/S009, Celebrex, (celecoxib, Searle)

Wednesday, February 7, 2001

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland



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C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

HARRIS: I would like to call the session to order. My name is Nigel Harris. I am Dean and Senior Vice President for Academic Affairs at Morehouse School of Medicine and I am also a rheumatologist.

Before we do the introductions, I am going to ask Ms. Reedy to read the statement.

Meeting Statement

MS. REEDY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions; in accordance with 18 United States Code 208(b), full waivers have been granted to Drs. Frank Harrell, Steven Nissen, Ileana Pina, M. Michael Wolfe and Allan Sampson.

Copies of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

We would, however, like to disclose for the record that Dr. Steven Nissen, Ileana Pina, H. James Williams and M. Michael Wolfe have interests which do not constitute a financial interest within the meaning of 18 United States Code 208(a) but which create the appearance of a conflict.

The agency has determined, not withstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Nissen, Pina, Williams and Wolfe may participate in today's discussion of Celebrex.

With respect to FDA's invited guest expert, there are reported interests which we believe should be made public to allow participants to objectively evaluate his comments. Dr. Byron Cryer would like to disclose that, in 1997, he received a research grant from Merck to conduct a small clinical study on rofecoxib. He has received consulting and speaker fees from G.D. Searle, Pfizer and Merck for work on celecoxib and rofecoxib. Additionally, he has previously been a consultant for SmithKline Beecham and Ortho McNeil.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves

from such involvement and their exclusion will be noted for the record.

With respect to all participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

I might add that the waiver criteria can be found at the FDA's site on the Web. I won't quote the law. That is too long.

DR. HARRIS: Thank you.

We can now begin with our introductions. I will start on my left with Dr. Cryer. If you can give your name and where you are associated

DR. CRYER: Byron Cryer, University of Texas, Southwestern Medical School, Dallas, Texas.

DR. WOLFE: Michael Wolfe, Boston University School of Medicine, Boston, Massachusetts.

DR. PINA: Ileana Pina, Case Western Reserve University, Cleveland, Ohio, Cardiology.

DR. NISSEN: Steven Nissen, Cardiologist, Cleveland Clinic, Cleveland, Ohio.

MS. McBRAIR: Wendy McBrair, Southern New Jersey Regional Arthritis Center at Virtua Health in New Jersey.

DR. WOFSY: David Wofsy, University of California, San Francisco, Rheumatology.

DR. CALLAHAN: Lee Callahan, University of North Carolina, Chapel Hill, Department of Orthopedics.

DR. HARRIS: I repeat that I am Nigel Harris, Morehouse School of Medicine, and Dean, Senior Vice President for Academic Affairs. And I should add, a rheumatologist.

MS. REEDY: Kathleen Reedy, Food and Drug Administration, Advisory and Consultants Staff.

DR. WILLIAMS: James Williams, University of Utah, Rheumatology.

DR. SAMPSON: Allan Sampson, Department of Statistics, University of Pittsburgh and currently on sabbatical as a visiting scholar, Department of Family Preventive Medicine, University of California at San Diego.

DR. ELASHOFF: Janet Elashoff, Biostatistics, Cedars-Sinai Medical Center and UCLA.

DR. HARRELL: Frank Harrell, Biostatistics, University of Virginia School of Medicine. I am a Consultant to CDER Biostatistics.

DR. WITTER: Jim Witter from the FDA.

DR. GOLDFIND: Larry Goldfind, FDA.

DR. BULL: Jonca Bull, FDA.

DR. DeLAP: Robert DeLap, FDA.

DR. HARRIS: Thank you.

We will now hear from Dr. Jonca Bull who will give

welcome and introduction.

Welcome and Introduction

DR. BULL: First of all, welcome. Thank you very much to our committee for coming here this morning. Please know how much we appreciate your willingness to share your time and your intellect to assist us in our deliberations on these important topics over the next two days.

Can we ever know enough about the safety of a drug? Can we ever know enough about the safety of drugs that have had widespread acceptance in the marketplace where rare events can become numerically significant numbers.

We are here today as part of a continuum of discussion on the safety profiles of two drugs that were approved in 1999 and that have literally had, I think, one of the most--as, I think, an article in USA Today asserted, some of the most successful launches of drugs in U.S. pharmaceutical history.

We ask that you deliberate carefully, think broadly and, again, welcome.

I would like to introduce Dr. Jim Witter who will be providing for you a regulatory and scientific background in the issues that we will be discussing over the next two days. Thank you.

MS. REEDY: I might comment that our podium is in this position for electronic reasons. We apologize for any

inconvenience.

Regulatory and Scientific Background

DR. WITTER: Good morning.

[Slide.]

I would like to thank, especially the members of the advisory committee, for taking time from their busy schedules to be here.

The discussion for the next two days, then, will focus primarily on the question of whether Cox-2 agents, as currently recognized by the division, are safer than Cox-2 nonselective agents, commonly called nonsteroidal antiinflammatory drugs or NSAIDs. In fact, some discussion will focus on whether these Cox-2 agents were studied at 2X dose and, if so, whether these superphysiologic doses are safer than NSAIDs at their conventional doses.

To help address the various aspects of safety, large and simple trials were conducted by both sponsors. The division is aware that it is not often that meetings to discuss issues of safety postapproval are discussions of improved safety. More often, it is, in fact, the opposite. So this is going to be a welcome discussion for the next two days.

[Slide.]

We thought it would be useful to set this in context. There is a rich history in this area and so we

thought a few minutes to set aside to put that in some kind of--put this meeting in context would be useful.

As we know, acetylsalicylate, also known as aspirin, was first synthesized and sold in 1899. About forty years later, there was the first evidence by endoscopy that this compound could damage the upper GI tract. About 30 years or so later, we started seeing the new safer NSAIDs being developed and approved.

In 1992 was the first widely held idea that Cox-2 was discovered, that, in fact, there was yet another target for these enzymes. Before that time, we thought there was just a single target. In 1998, we had the first advisory committee for the first Cox-2 and it was approved in that year. Today, we are discussing the first large and simple safety trials.

[Slide.]

The FDA has also been involved with the help of the commit
tee, as today, for quite a while. Back in December of 1986, we discussed the databases that went into the formulation of the GI paragraph. In October of 1995, there was a series of two-day meetings where we discussed the revision of the NSAID class label and also had a citizen petition for the removal of peroxicam from the marketplace.

In March of 1998, we had, before the approval of

any of these compounds, a meeting to discuss some of the safety issues that we felt were emerging with these particular compounds. As said before, in December of 1998, we had the advisory committee for Celebrex followed shortly thereafter, in April of 1999, by the advisory committee for the approval of Vioxx and then today and tomorrow, again, the long-term safety studies with these compounds.

[Slide.]

As mentioned, and what I will do is use the previous slide as kind of the focus for the rest of the talk, the GI paragraph, as it exists, points out to us that there are serious GI toxicities associated with these compounds and they can occur both with and without warning to the patients.

Only one in five, or about 20 percent, who develop these serious upper GI events, have any kind of warning symptoms. The GI paragraph notes that patients at risk include those who have a history of prior ulcer or a bleed, are older, are on certain medications or who are in poor health.

It notes that these trends basically continue and that the best way to minimize the risk is to use the lowest dose for the shortest period of time.

[Slide.]

The events that are referred to are often referred

to as clinically relevant events in terms of the upper GI tract and, as stated, again in the GI template and the GI paragraph, it has been demonstrated that upper GI ulcers, gross bleeding or perforation caused by NSAIDs appear in approximately 1 percent of patients treated for three to six months and in about 2 to 4 percent of the patients treated for one year.

In fact, estimates from the ARAMIS database note that NSAID-induced gastropathy may result in 107,000 hospitalizations and 16,500 deaths on an annual basis.

[Slide.]

So NSAIDs have a certain safety toxicity profile which we have become familiar with. As I have indicated, they are both dose and duration dependent and they involve a variety of organ systems and are reported to us as adverse events, either mild, moderate or severe, as serious adverse events or as deaths.

[Slide.]

The NSAID template, then, is a more general structure for how we write these labels for NSAIDs. It describes, among other things, precautions, warnings and adverse reactions involving, as we just discussed, the GI tract, but also the liver, the kidney. It describes anaphylactoid reactions, immunologic effects, effects on skin and others.

[Slide.]

The template, in terms of the liver, notes the metabolic effects of hepatic insufficiency. It notes elevations of the enzymes and sometimes, in 1 percent of the cases, it notes that these can occur up to three times the upper limit of normal. It also points out that there are rare cases of severe reactions involving jaundice, fulminant hepatitis, liver necrosis and hepatic failure and, in fact, some of these can be fatal.

[Slide.]

It notes, in terms of the kidney, that there are certain pharmacodynamic effects of renal failure or dehydration, that these compounds can have effects on blood pressure, particularly with regards to hypertension, that these compounds, NSAIDs, can cause fluid retention and edema in some settings and can be associated, again, with severe reactions such as renal papillary necrosis, interstitial nephritis and renal failure.

[Slide.]

In terms of skin, the template notes that there are reactions such as photosensitivity, urticaria and severe reactions including Stevens-Johnson syndrome, toxic epidermic necrolysis and erythema multiforme which, again, can be fatal.

[Slide.]

For the safety risks, what are the benefits. The efficacy of NSAIDs can be summarized as follows. For OA, they have been indicated for the treatment of osteoarthritis. This is for the signs and symptoms, not for structure or disability as it currently exists in the draft OA guidance document.

NSAIDS are also indicated for the treatment of rheumatoid arthritis, again for the signs and symptoms not for structure or improvement in function or remission claims as exist in the current RA guidance document. They are indicated for acute pain and dysmenorrhea as well as other indications such as ankylosing spondylitis, gout, among others.

[Slide.]

As indicated, there has always been a lot of hope surrounding the Cox-2 field. In fact, in the Wall Street Journal, in '96--this has been shown before at a prior meeting--it was thought that these compounds could not only ease pain but actually slow the disease's debilitating progression. So there has always been a lot of excitement.

As indicated, we had a meeting before approval of any of these compounds back in March of 1998. Primarily, it was to discuss the safety issues and what we were hoping would be the approved safety profile of these types of compounds. And then, as now, we presented to our committee

certain questions.

For example, we asked them to comment about the degree to which endoscopic studies can distinguish between the currently available NSAIDs and the degree of correlation with clinical outcomes. Some of the comments at that time were that endoscopic studies were generally underpowered to answer these questions we had posed, that the measurable--in this case the endoscopic--might drive out the important--in this case, the clinical outcomes.

There was a discussion about the role of endoscopy as a surrogate--how it might turn out to be for the long-term outcomes of interest.

[Slide.]

We, at that meeting, discussed, then, in terms of the GI warning, what kind of changes might be effected with the Cox-2 agents. We discussed, for example, would removal require the concept of equivalence to placebo, which would have to be mutually defined and agreed to, or, if we could be discussing a major revision, what would that include; for example, substantial reproducible evidence of superiority over NSAIDs and that would include, undoubtedly, endoscopic and clinical endpoints.

The discussion was how many NSAIDs would it take. Would it take three? And we would have to obviously agree on which NSAIDs we decided to study.

[Slide.]

At that meeting, we also discussed the importance of words--for example, the idea of being equivalent to placebo. We had a rather lengthy discussion about saying that two treatments are similar does not necessarily mean that they are the same. From a statistical standpoint, failing to show a difference is not showing equivalence. In fact, equivalence requires that the hypothesis, treatment X and Y are different, be rejected in a trial designed specifically for that purpose. And we talked about that.

[Slide.]

We also talked about whether we could best view the potential safety advantage of Cox-2 agents on a mechanistically based origin. For example, on one extreme where Cox-2 was felt not to be present in the platelets, we would have one result. On the other hand, where Cox-2 was present, such as in kidney, we would have yet an opposite result.

It was clear to us that this field was evolving rapidly and targets were appearing where they initially hadn't been found. So we might then be in a position where Cox-2 may be present in some situations and it may not be present in other situations. The stomach may be an example of that and we might, then, get an intermediate result.

[Slide.]

If then, again at this meeting, discussing if the Cox-2 agents were different, were they, in fact, representatives of a different class. And we discussed how many agents it would take to define that class. We were curious, in terms of how more potent inhibitors, if they were to be developed, how they might fit into this scheme.

We, again, discussed the label, whether we would revise the current NSAIDs template or, in fact, write an entirely new label, depending on the data. There was always the question of, in these trials, whenever we were discussing results, how many of the results were actually testing the drug, the theory of how the drug should be working, or a combination of both.

[Slide.]

We always had an eye to the future, wondering about other indications. For example, as I alluded to earlier, any kind of structural modification, OA or RA. We had been hearing about prophylaxis for colon cancer and we had also been hearing about prophylaxis of Alzheimer's disease.

We were certainly aware, and would not have been surprised, if we would have seen some unique adverse events associated with these particular compounds. Of course, we were very interested in the safety and efficacy in children because NSAIDs had typically not been studied in an

organized fashion.

[Slide.]

In December, then, at the end of 1998, celecoxib, or Celebrex, was submitted and discussed. It was, as I have indicated at the bottom there, a large submission, lots of information. From that information, we were able to glean the following.

[Slide.]

In terms of OA, Celebrex was found to be at doses from 100 to 200 milligrams BID more effective than placebo. However, it did not appear that there was any obvious efficacy advantage of the 200 milligram BID dosing and it appeared that 100 milligrams BID was about the same as 200 milligrams on a daily basis.

The efficacy, in terms of the treatment for OA, was comparable to naproxen at 500 milligrams BID and we noted, in the long-term safety trials that were part of the NDA, that most patients, in this case, about 70 percent, increased their dose in the open-label experience and this has been known in the literature as the dose creep.

[Slide.]

In the NDA, then, for Celebrex, it was also indicated for treatment of RA, at doses from 100 to 400 milligrams BID, found to be more effective than placebo. There was no obvious, again, efficacy advantage of going up

to the higher dose of 400 milligrams BID, though. Once more, comparable to naproxen at 500 milligrams BID and, again, we noted that, in the open-label experience, about 70 percent of patients increased their dose, again an example of the dose-creeping phenomenon.

[Slide.]

The NDA did not allow us to give the indication for treatment of acute pain and dysmenorrhea.

[Slide.]

So we discussed, at that time, the Cox-2 hypothesis and wondered how Celecoxib would fare against that. It was really a representative of that, particularly as we discussed efficacy because, as indicated, the analgesic efficacy appeared to be less than NSAIDs for acute pain. So we wondered if the problem was really with the models that were selected in the particular NDA.

We wondered if it was due to the nature of acute versus chronic pain and did this have something to do with the induction of Cox-2, or we wondered whether this was related to the potency or selectivity of celecoxib, among other reasons.

We also discussed that, in these studies, there didn't any obvious efficacy advantage compared to NSAIDs for OA and RA, but we wondered what would happen in long-term trials.

[Slide.]

Then, as indicated later on, the NDA for Vioxx was submitted and, in there, was sufficient information for labeling for OA and it was found that, at doses of 12.5 and 25 milligrams on a daily basis were better than placebo.

Once more, there didn't appear to be any obvious efficacy advantage of the higher dose at 25 milligrams daily. The efficacy was found to be comparable to ibuprofen at 800 milligrams TID and diclofenac 50 milligrams TID and there was no information for us to get any idea of what would happen in an open-label experience.

[Slide.]

For RA, there was no data submitted in the NDA.

[Slide.]

For pain, Vioxx was indicated for acute pain and dysmenorrhea at doses of 50 milligrams daily and, in five-day studies, was found to be more effective than placebo.

[Slide.]

So, at this point in time, it appears that, in terms of efficacy for COX-2 agents like NSAIDS, they are indicated for the treatment of signs and symptoms of osteoarthritis. This is both, again, for Celebrex and Vioxx. They are indicated for the treatment of rheumatoid arthritis, and this is only for Celebrex, at what is now called the 'x' dose.

They are indicated for the treatment of acute pain and dysmenorrhea. This is only for Vioxx. They are indicated also for the treatment of a rare form of cancer known as familial adenometous polyposis, or FAP. This is only for Celebrex and this is now at what we call the 2X dose as adjunctive therapy in this particular condition.

[Slide.]

So, despite their long history of usage, no NSAID has been tested in a large and simple long-term safety trial at doses exceeding the upper limit of the approved labeling in arthritis, particularly at the 2X dose. So we are really going into uncharted waters here. Again, we are always looking to the future.

Thank you.

DR. HARRIS: Thank you very much, Dr. Witter. We will have a discussion this afternoon. We are going to limit any questions the committee might have to just clarification, or whether or not there is any clarification required with respect to Dr. Witter's presentation.

Seeing none, we will move to the next item on the agenda and that will the presentation by G.D. Searle and Company. Dr. Philip Needleman will introduce.

G.D. Searle and Company Presentation

Introduction

DR. NEEDLEMAN: Thank you very much. Good

morning.

[Slide.]

We have been asked by the agency to continue to extend the tutorial points about some aspects of the history and discovery of COX-2 inhibitors and set a context for today's review.

[Slide.]

This will be the agenda that we will proceed under. I will start with the introductory remarks. I am the chief scientist of Pharmacia and the Chairman of Research and Development.

[Slide.]

In 1990, based on our discoveries, we discovered the existence of a novel isoform of cyclooxygenase, the enzyme that produces prostaglandin. We discovered that the newly produced enzyme was intimately associated with inflammation and pain and swelling.

So we set forth this hypothesis that said that there were two enzymes. One was a housekeeping enzyme, a constituent of one, which maintained a physiological function, and those functions were especially prominent in gastrointestinal tissue where the prostaglandin was involved in the synthesis of mucus which protects the stomach and intestine from acid and enzymes. it was also especially present as an enzyme in platelets, and that was COX-1.

We further hypothesized that all existing NSAIDs, aspirin-like drugs, were nonselective and inhibited both enzymes, and indeed these are potent agents and their mechanism of action was the treatment of prostaglandins produced at the site of inflammation.

Their problem and limitation was they also produced mechanism-based side effects by blocking prostaglandins especially in the gastrointestinal tract and in platelets.

This hypothesis was the primary drive of our enormous effort to seek out, and what eventually led to, the discovery of celecoxib Celebrex to achieve the efficacy of NSAIDs, but with a far superior GI profile.

[Slide.]

Now, in the 1998 NDA, we established that here a dose response curve in rheumatoid arthritis patients was fully equivalent in efficacy to the widely used naproxen without evidence of endoscopic damage here being similar through 400 mg BID to placebo, but statistically well less than the 25 percent incidence of endoscopic ulcers induced with naproxen and all the other NSAIDs.

[Slide.]

So, for a perspective, as you just heard, it was reviewed in December of '98 and approved by the end of December 1998, and it was based on its demonstrated

endoscopic upper GI safety compared to conventional NSAIDs.

For the context which you just heard, endoscopy was regarded as a surrogate, so indeed the warning labels for Celebrex reflected that NSAID template. So, this large, well-designed trial was designed to achieve really greatly expanded and clinically meaningful GI safety with the design intended to go for differentiation of that warning label based on the superior safety of Celebrex versus NSAID.

[Slide.]

Now, the class trial's primary objective was the GI safety, but inherently we will able to comment on the systems you saw reviewed - the renal, the cardiovascular, and so on.

This proved to be a quite complicated and rigorous trial. We chose and worked actively at all stages of this to frequently interact and collaborate with the agency, and we designed a trial that really followed the practice of medicine, so we enrolled both OA patients and RA patients, we used multiple NSAIDs, and we allowed cardiovascular use of low-dose aspirin because this age population in practice was using these for cardioprotection.

We used two NSAIDs, agreeing with the agency that we should include ibuprofen because it was regarded as a safer NSAID, and so we wanted two NSAIDs and really to compare to the one that had the higher safety.

Furthermore, as you heard, kind of in an unprecedented way, we used a dose that was 2X the maximum dose in rheumatoid arthritis and was actually 4 times the dose, the maximally achieved dose used for Celebrex in arthritis, but we compared that with the commonly used doses, not even the maximum doses, of the ibuprofen and the diclofenac. So, it was an exaggerated trial to really see the scope of the GI safety and have a long term sense of their utility and their improved potential.

[Slide.]

So, in the context that we were asked by the agency to then say, okay, what do you know in 2001 about the COX-2 hypothesis that you didn't know in 1990 and really started the large program.

Well, the bulk of the information is fundamentally the same. Indeed, there are two enzymes. It is clear in COX-1 that it is restricted to the stomach, the intestine. In the kidney it maintains renal blood flow. The platelets are only COX-1, and platelets are cells that don't have a nucleus, so if you use an aspirin-like drug, you will irreversibly block that COX-1. NSAIDs, all NSAIDs hit COX-1, as well as COX-2, but those are transient inhibition.

It also became clear, and we were asked to talk about this role of COX's in platelets and endothelium. The endothelial cells and the blood vessels, smooth muscle cells

are all normally constituents of COX-1. Their product is PGI2.

Now, on the COX-2 side, indeed, inflammation of all sorts is associated with COX-2 expression, and it is an enzyme that is induced and it is not normally there. We now know that nearly every epithelial tumor expressed COX-2, in precancerous steps, at cancerous, and in metastatic stages, and as Jim Witter showed you, we achieved approval of the pretreatment of a regression of precancerous polyps, the familial adenoma polyposis, and large trials are underway in colon cancer and other cancers.

It is now clear in the next three that COX-2 also exists in the physiological maintenance especially in some species of kidney function. It is present constituitively in the central nervous system, and it plays a large role in female reproduction.

Finally, endothelium has inducible enzymes and in certain kinds of treatments, there can be some induction of COX-2. So, then this is the setting for the CLASS trial where you have that large database to look back to see did you unmask unique side effects.

[Slide.]

The CLASS trial then definitely will allow us to shed light on the roles of COX-1 and COX-2 on the GI events and actually on the blood loss which we think also reflects

GI events.

We have data to really possibly comment about the implications of low dose aspirin, because in the end now we have a large prospective trial with a large database about low dose aspirin, and could at least comment about the possible issues about cardiovascular, renal, and thrombotic events.

What this trial won't add to is this is largely an aged population, so there won't be evidence about female reproduction. A CNS trial has completely different parameters and endpoints, and wasn't doable, and again, the cancer trials are completely different trials, and the long term trials are three years in treatment. So, we can comment in these two areas.

[Slide.]

We were asked to talk about--and it is an important point--about then the use of low dose aspirin, so we are talking about 325 milligrams or less. Aspirin, because it is capable of acetylating a serine in the active side of cyclooxygenase, irreversibly inhibits that enzyme and platelets lacking the nucleus can never reconstitute new enzyme, so one dose of aspirin permanently wipes out platelets. That is by blocking the cyclooxygenase which makes thromboxin, which is the aggregator constrictor substance. Similarly, that is the mechanism basis of the

increase in bleeding potential.

So, in '98 when this was approved, I think there were 18 or 20 NSAIDs proved to be nonspecific, very potent on COX-2, very potent on COX-1. All NSAIDs transiently inhibit platelet COX-1 and the thromboxane production, and there is no difference if it's ibuprofen, diclofenac, or naproxen.

Now, aspirin also has the property of being a direct irritant and damaging the GI mucosa. Importantly, in a recent New England Journal of Medicine paper--and there is a number of important papers--low dose aspirin, this 325 milligrams or less, shows the increased risk of GI ulcer complications on its own.

So, with this context, we could take a look and see what the CLASS data says about the GI side effects of aspirin.

[Slide.]

Now, in the renal system, it is clear now because you have the cDNA probes and the antibodies that both isoforms are expressed constituitively, that is, it is normally there and is turned on inactive.

The confusion starts to occur when you look at the anatomical distribution of the enzyme. The most studies were in rat especially and in dog where there was high expression in the kidney at the sites of renin production,

and indeed you can see COX-2 effects. On the other hand, primates and humans don't have expression in the same site, so that is not so clear.

The database did not distinguish between Celebrex and NSAIDs, so in terms of increased edema, both Celebrex and NSAID had a response, but Celebrex did not exhibit a dose-dependent increase in that response.

[Slide.]

Importantly, we were asked about the cardiovascular and thrombosis. As you know, low dose aspirin is especially used in the treatment, in the secondary prevention of myocardial infarction, and this mechanism-based response is due to the irreversible inhibition of the platelet COX-1 to block thromboxin.

So, there is clear and substantial evidence that low dose aspirin is a benefit during an acute myocardial infarction, during unstable angina, and clearly a benefit in the secondary prevention of myocardial infarction.

In terms of primary prevention, it is a marginal case and there is no clear demonstration anywhere near as clear as the secondary prevention.

Now, in that context, we will remind you that blood vessel smooth muscle and endothelium produces prostacycline PGI2 predominantly from COX-1. That is the opposite of thromboxane in the platelet which causes

aggregation. PGI2 is anti-aggregatory and vasodilate.

Now, it is normally only COX-1, but part of the issue with that could be turned on there, so you are thinking about the site of interaction in blood vessels of platelet and endothelium.

What you have to remember, though, is the endothelium makes continuously prodigious amounts of nitric oxide which in its own right is a very potent antithrombotic and is a potent vasodilator, and nitric oxide sensates in blood vessel is not inhibited by NSAIDs or COX-2. So, the aspirin story or NSAID story doesn't affect the endothelial nitric oxide.

[Slide.]

Now, to illustrate the doses in patients that were COX-2 selective, from the NDA I could show you data on platelet aggregation, so this is platelets removed from patients and treated with arachidonic or other stimuli to measure aggregation.

You see placebo in the white bar. Here, we went to 600 mg twice a day, well above even the exaggerated dose we used in this CLASS study, and you see no inhibition of platelet aggregation. Here, you see inhibition by diclofenac, and you can show full-range dose response curves through the 1,200 mg, and it is COX-2 selective dose without inhibition of COX-1.

[Slide.]

Now, that is pertinent and the reason this is a question at all is this data was published by McAdams, it is from the Garrett Fitzgerald data in which they looked at human urinary PGI2 metabolites, PGIM, and looked at placebo, does of Celebrex that were COX-2 selective and didn't affect COX-1, and looked at doses of ibuprofen.

What you see is a suppression of these PGI metabolites. Since that was a dose that was COX-2 selective, that suggested that there was some COX-2 generated PGI2. Now, we don't know if that is from the epithelium because it is urine, but then this is the basis of the hypothetical consideration.

[Slide.]

So, the question is, is that PGI2 inhibiting platelet aggregation, and this work suggests if it was endothelial, which we couldn't tell, that you would be affecting that PGI2 and endothelium.

[Slide.]

So, here is a cartoon of their hypothesis. If thrombosis is on this balance beam, it is the platelet COX-1 that is causing aggregation, and it could theoretically be the prostacycline, PGI2, made in the endothelial cell.

Since NSAIDs would block both, the beam would stay balanced and there would be no effect on thrombosis,

however, if COX-2 inhibitors were around, you would suppress this, thromboxane could be dominant, and you would have the potential for the risk of a thrombotic event.

So, if the hypothesis is correct--and remember by and large endothelial cells still are predominantly COX-1, if it is correct, then, the expected effect of COX-2 inhibitors would be similar to patients not taking the low dose aspirin in an at-risk population.

[Slide.]

So, what about the CLASS data? What can we say about the potential for assessing the risk? The cardiovascular benefit of aspirin--and now here we are even talking about the secondary prevention because there is no case for primary prevention--the question was the ability of aspirin to reduce the primary event or, similarly, what is the ability of a COX-2 inhibitor to cause a cardiovascular event.

If you look at something like Physicians Health Study, the sample size required would be greater than 20,000 patients for five years to find the event. So, therefore, the CLASS trial, we had 8,000 patients, but only 4,000 patients on Celebrex, was never large enough to detect such a small cardiovascular event due to COX-2 inhibition of endothelial cells.

In other words, with this sample size, you can't

show a mechanism-based event, a cardiovascular event. However, the CLASS trial was large enough for general cardiovascular safety and renal safety, or in other words, if you would see a thrombotic event with this small of a trial, it can't be mechanism based, it would have to be molecule based because the trial is inadequate in size.

[Slide.]

So, in summary, and what we will review with you today, is we feel that there a preponderance of clinical data which exhibits the safety of COX-2 inhibition and Celebrex compared to NSAIDs which would warrant the change of the NSAID platelet.

That is built on now this continuum of data, started with the endoscopy of nearly 5,000 patients in the NDA, it's this 8,000 patient trial with evaluation of ulcers and complications in the CLASS trial, and it's this very large postmarketing surveillance.

We looked at the exaggerated doses, the 2 to 4X of the RA and OA dose, and in that trial, as you heard asked before, there was no new safety signal even in this long-term trial with the exaggerated dose, and we think that Celebrex did not increase the thromboembolic events compared to NSAID, and that was true both in the absence and the presence of aspirin.

[Slide.]

So, with this as a setting, we will lay out the context of the clinical trial and the data, and we will start with Dr. Steven Geis.

UGI Safety Profile of NSAIDs and Celecoxib:
Rationale for CLASS Study

DR. GEIS: Good morning.

[Slide.]

In my presentation, I will review the history of our understanding of NSAID-associated upper GI toxicity and review the prospective trials that were used to evaluate the upper GI toxicity of NSAIDs, and then finally discuss the upper GI safety data on celecoxib that we had at the time of the submission of the NDA.

[Slide.]

In reviewing the NSAID-associated upper GI toxicity, I first want to review the various types of toxicity that have been appreciate over the years, incidence of this type of damage, and then to define who are the patients at risk.

[Slide.]

Now, in the 1970s and 1980s when NSAIDs became widely used to treat the approximately 44 million arthritis patients in the U.S., physicians began to be aware that patients were, in fact, developing side effects associated with NSAIDs, and these were predominantly upper GI in

nature.

These included symptoms, but the symptoms also evolved into symptomatic ulcers. These ulcers, in turn, could become complications, that is, the ulcers could bleed, they could perforate, or, in fact, form outlet obstruction in the stomach.

[Slide.]

Now, this slide shows the type of endoscopic appearance of an ulcer that a patient might have had during that time. That is, the patient would have a symptom, the clinician would perform an endoscopy and observe this type of an ulcer which, in that terminology, is called a symptomatic ulcer.

[Slide.]

In some cases, the ulcer was proximal to a blood vessel and if the lesion progressed, the blood vessel could be eroded and we would have a bleeding ulcer or an ulcer complication.

[Slide.]

Also, the ulcers could erode completely through the wall of the stomach or the intestine forming a perforation, and as everyone can see from this type of typical x-ray from a patient who has had a perforation, we have free air under the diaphragm.

[Slide.]

So, as time progressed, clinicians became aware that there was a spectrum of NSAID-related upper GI injury which ranged from symptomatic ulcers and easily could form an ulcer complication, the bleed or the perforation.

[Slide.]

Now as our understanding progressed, certain acronyms and definitions began to evolve and develop and are seen in the literature. Over time, symptomatic ulcers, perforations, and bleeds became referred to as PUBs, whereas, perforations, outlet obstructions, and bleeds became referred to as POBs.

In my presentation and those of my colleagues today, we won't be using this terminology, we will be referring to NSAID toxicity as symptomatic ulcers or ulcer complications.

[Slide.]

To determine an understanding or to establish an understanding of the magnitude of the problem, over the years observational cohort and retrospective cohort or case controlled studies were performed, and in these studies, the investigators examined hospital records for diagnoses of patients who had symptomatic ulcers or ulcer complications, and then looked to see if there was an association with NSAID use. In this manner, they were able to establish what is really the rate of these types of toxicities with NSAIDs.

[Slide.]

They found--and this was repeated by several investigations, and as Dr. Witter pointed out--that it was established that the overall incidence of the symptomatic ulcers and the ulcer complications was on the order of 2 to 4 percent per year. These retrospective analyses also gave us evidence that some of the ulcer complications were symptomatic, but also some of them were not symptomatic, that is, there was no heralding symptom prior to the actual bleeding or the perforation taking place.

It really depends upon what study you read what is the percentage of these types of toxicities that are actually asymptomatic complications, and it can range anywhere as low as 10 percent up to 60 percent depending upon the study.

The retrospective studies also allowed us to look at what is the background rate of this type of toxicity in patients not using NSAIDs.

[Slide.]

As we see here from the work of Dr. Singh and Dr. Perez-Gutthan, that in NSAID users indeed the incidence of ulcer complications by their studies was on the order of about 1.3 to 1.7 percent per year, but in non-NSAID users the rate was about 6-fold lower, on the order of about .03 percent per year, so we knew there was a background rate,

and in NSAID users, these very serious complications occurred about 7 times more frequently.

[Slide.]

Also, investigators were able to estimate what was the mortality due to the GI toxicity of NSAIDs, and here we show the Aramis database, as well as the Tennessee Medicaid database. The Aramis database predicted that the number of deaths in the U.S. due to NSAID GI toxicity was about 1.3 per 1,000 patient years, and then estimating that based on 13 million patient years of exposure in the U.S., this would equate to approximately 16,500 deaths per year in the U.S. alone due to NSAID GI toxicity.

In the Tennessee Medicaid database, they estimated that in the elderly, defined as 65 years of age or older, that the rate of death due to NSAID GI toxicity was about 1.4 per 1,000 patient years. Estimating the patient years of exposure in the elderly of about 2 million, they estimated that there is about 3,300 deaths in the U.S. in the elderly due to NSAID toxicity.

[Slide.]

The retrospective studies also gave us an idea of who are the patients at risk of such problems. Although there were many risk factors identified, those which consistently were the most correlated with the complications were increasing age, a history of an ulcer or GI bleeding,

the dose of the NSAID, and the duration of the NSAID use, as well as the use of low dose aspirin.

[Slide.]

This slide shows the work of Perez-Gutthan, which shows the odds ratios for ulcer complications as a function of age. What we see is in females and in males, that with increasing age, in patients not taking NSAIDs, there is an increased rate of developing or an increased risk of developing an ulcer complication. However, in the NSAID users, that rate is about 5 times higher in all age groups. So, although there is a correlation between age and the likelihood of developing a complication, even the young patients are on NSAIDs are at risk of developing a complication.

[Slide.]

Here, we show the work of Dr. Weil which looked at the risk of upper GI bleeding related to prophylactic aspirin use. The odds ratio ranged from 2 to 4 at doses of 75 mg to 300 mg, all of which are considered prophylactic doses of aspirin.

[Slide.]

The work of Henry looked at the risk of upper GI bleeding of various types of NSAIDs. In this work, they used ibuprofen as the reference NSAID, so if you will, they considered ibuprofen to be the safest although we know that,

in fact, is not the case.

Nevertheless, using that as the reference, they found that the risk of upper GI bleeding with all the NSAIDs was high and was certainly statistically higher than that seen with ibuprofen based on this study.

[Slide.]

So, in conclusion, based on the retrospective studies that were conducted and the observations made by investigators, it was found that symptomatic ulcers and ulcer complications really are on a continuum of GI toxicity, all NSAIDs are associated with this type of toxicity, and approximately 16,500 deaths occur per year in the U.S. due to NSAID toxicity.

[Slide.]

Now, I would like to look at the prospective trials that evaluated NSAID upper GI safety, looking at the endpoints of endoscopic ulcers and the one study that used ulcer complications as an endpoint.

[Slide.]

Now, if we can refer back to the definitions once more, so we now have symptomatic ulcers and endoscopic ulcers. Symptomatic ulcers are a form of upper GI toxicity encountered in clinical practice, and these are identified by a "for cause" endoscopy.

On the other hand, endoscopic ulcers are measures

of GI toxicity in clinical investigations, and these are identified by a scheduled endoscopy in the course of a clinical trial.

[Slide.]

The endoscopic ulcer studies really confirmed what we observed in our retrospective assessments, so here we show the prevalence of endoscopic upper GI ulcers for various NSAIDs, and what is seen is that all NSAIDs were associated with upper GI ulceration at a rate of about 20 to 30 percent.

This work was confirmed by a variety of investigators who did similar types of endoscopic studies and found that NSAIDs produce a point prevalence of ulcers in the stomach and the duodenum ranging anywhere from 5 percent up to as high as about 30 percent.

[Slide.]

The endoscopic studies also confirm the relationship of GI toxicity with NSAIDs and age. Here, we show the work of Cheatum showing that the point prevalence of ulcers as a function of age increases, but importantly, even the younger patients in the range of 30 to 39 years old did have a high incidence or a high point prevalence of NSAIDs ulceration.

[Slide.]

As Dr. Witter pointed out, the question became:

Are endoscopic ulcers really surrogates of ulcer complications?

[Slide.]

Actually, it seemed to make sense. NSAIDs reduce mucosa prostaglandins, and we know thereby causing ulcers. Ulcers can result due to erosion through a vessel or erosion through the wall of the stomach of the duodenum, and bleeding perforation or outlet obstruction, but we couldn't be sure that the endoscopic ulcers really did predict this.

Where we really found that to be true was in the development program for misoprostol, which is a synthetic prostaglandin, and based on this program, we were able to show a relationship between endoscopic ulcer data and ulcer complications.

[Slide.]

I would first like to show you the results of an endoscopy trial using misoprostol. This was a one-year study in patients with osteoarthritis or rheumatoid arthritis.

All patients were endoscoped at baseline and then endoscoped at various points during the trial. Half the patients received an NSAID plus placebo, whereas, the other patients received the NSAID plus the synthetic prostaglandin.

[Slide.]

This slide shows the results of that study. Over a one-year period, the incidence of ulcers in patients who received the NSAID plus placebo was about 30 percent. The patients who received the NSAID plus the synthetic prostaglandin was reduced in half to 15 percent, so a 50 percent reduction.

[Slide.]

We then conducted the MUCOSA trial, and this was to look at the effects of the synthetic prostaglandin on clinically relevant outcomes. It was a prospective, randomized, double-blind trial where the primary endpoint now was ulcer complications defined as bleeding, perforation, and obstruction.

[Slide.]

It was designed to parallel normal medical practice in that scheduled endoscopies were not performed, they were only performed for cause.

[Slide.]

This slide shows that we prospectively formed a GI Events Committee that provided definitions of what an ulcer complication would be in the MUCOSA trial, and these definitions really became the basis of definitions we use in the celecoxib program.

[Slide.]

Here, we show the results of the MUCOSA trial.

Over time, the incidence of ulcer complications in the NSAID-treated group increased, and those who received misoprostol plus the NSAID, the rate was reduced by approximately 50 percent.

[Slide.]

So, these prospective studies taught us that endoscopic ulcers and ulcer complications really are reliable endpoints for investigating GI safety, and endoscopic ulcers are indeed predictive of ulcer complications. The most important information that confirms this is that exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by approximately 50 percent.

[Slide.]

Now, I would like to follow up on what we knew about the upper GI safety of celecoxib in the NDA in 1998 using endoscopic ulcers, as well as ulcer complications as endpoints.

[Slide.]

At that time, we had performed endoscopies in over 4,700 arthritis patients. The results of the trials showed us that the incidence of upper GI ulcers was similar to placebo, and this was replicated, and statistically lower compared to traditional NSAIDs, such as naproxen, diclofenac, and ibuprofen.

[Slide.]

This slide shows the results of two of the studies, one of which Dr. Needleman previously described. There were three-month endoscopy trials. One was in OA patients, one was in RA patients, and each involved over 1,000 patients.

We compared the incidence of ulcers in placebo to celecoxib and then the NSAID naproxen. Celecoxib was similar to placebo at all doses even at the high dose of 400 mg twice a day, which is much higher than the approved therapeutic doses for OA and RA, and was statistically lower than that seen with naproxen.

[Slide.]

This slide shows one of the studies that was submitted at that time, which was a six-month endoscopy trial, comparing celecoxib to diclofenac. Once again, we showed a lower incidence of upper GI ulcers with celecoxib compared to diclofenac.

[Slide.]

In the program for celecoxib, we also looked at analysis of upper GI ulcer complications. Let me describe the methodology for collecting that data briefly.

We formed an external GI Events Committee that established criteria or definitions for upper GI complications, and this was defined prospectively.

The data then came from 14 randomized controlled

trials and one open-label trial, all of whom involved OA and RA patients. Patients who the investigators thought might be having an ulcer complication were then submitted to the GI Events Committee, who based on their definitions determined whether or not a complication really had or had not occurred.

In this whole process, the GI Events Committee was blinded to the trial and blinded to the study drug that the patient was on.

[Slide.]

The definitions of ulcer complications were similar to MUCOSA and are shown here.

[Slide.]

Also, these controlled trials were actually very extensive. They involved over 11,000 patient. The open-label trial involved over 5,000 patients. The controlled trials were 12 weeks in duration, the open-label two years, and the doses of celecoxib ranged from 200 to 400 mg per day.

[Slide.]

This slide shows the results of this analysis. From the controlled trials, in the NSAID-treated patients, the ulcer rate, the annualized ulcer rate was about 1.7 percent, with celecoxib it was only 0.2 percent, again, about a 7-fold reduction and similar to what was seen in

placebo and similar to what was seen in the literature for the background rates.

In the open-label trial, we also showed an incidence or an annualized incidence of about 0.2 percent.

[Slide.]

So, our conclusions at that time were that the incidence of endoscopic ulcers with celecoxib were similar to placebo and lower than NSAIDs, that endoscopic ulcer data were, in fact, predictive of the ulcer complication data, and that there was a lower incidence of ulcer complications with celecoxib compared to NSAIDs.

[Slide.]

However, the generalizability of the ulcer complication data was uncertain at that time because in the 14 randomized trials or controlled trials, many of these trial were endoscopy studies in which the patients were proven to be ulcer free by endoscopy at the start of the study.

So, about 40 percent of the patients in the analysis were really ulcer free, and the question was, well, is that data generalizable to the entire population, and in addition, most of the studies were three months in duration.

[Slide.]

So, this became the rationale for conducting the CLASS trial. We wanted to step forward and do a rigorous

assessment of the upper GI safety of celecoxib using clinically relevant outcomes in a patient population that fully represents the intended population and also to observe this with chronic exposure of celecoxib.

[Slide.]

Therefore, in brief, the design was a large prospective study. We wanted it to mirror normal medical practice, that is, endoscopies were performed only for cause. We wanted it to include a broad spectrum of patients, OA and RA patients.

We included high risk patients, that is, those who had comorbidities and those who were using low dose aspirin. As Dr. Needleman pointed out, we used the dose of celecoxib which was 400 mg twice a day, 4 times the OA dose and 2 times the highest RA dose, and the duration of the trial extensive. Patients were allowed to participate for up to 15 months.

I would now like to turn the podium to Dr. Lefkowith, who will review the trial in more detail and the results.

Safety Profile of Celecoxib:

CLASS, Long Term Safety Trial

DR. LEFKOWITH: Good morning.

[Slide.]

The celecoxib long-term arthritis safety study, or

CLASS for short, was performed to further explore the GI and general safety attributes of celecoxib.

[Slide.]

Before sharing with you the results of this landmark clinical trial, I would like to review for you the elements of study design. As the speakers before me have indicated, this was intended to be a "real world" study in that clinical practice conditions were reproduced as closely as possible.

Accordingly, the full spectrum of arthritis patients were enrolled, patients with OA, as well as RA. Moreover, patients were allowed to use low dose aspirin. Cardiovascular disease is a common comorbidity within the arthritis patient population.

Moreover, this was a stringent test of safety in that celecoxib was administered at 2 times to 4 times the RA and OA doses that were shown to be maximally effective, and compared to both ibuprofen and diclofenac, widely used NSAIDs. Again, ibuprofen has been regarded as one of the safest of the conventional NSAIDs.

[Slide.]

In discussing the design elements of the trial, I would like to review for you briefly the study objectives, the protocol design, the analytic plan, as well as the oversight committees and their function, these oversight

committees supervising the trial performance.

[Slide.]

The objectives of the trial were 3-fold. Celecoxib was to be compared with NSAIDs consisting of ibuprofen and diclofenac with respect to the incidence of ulcer complications and symptomatic ulcers. Moreover, the study intended to examine for risk factors for such outcomes, and for the effect of such risk factors on outcome.

Specifically included was an analysis of aspirin as a risk factor. Finally, the study was intended to compare the general safety and tolerability of celecoxib to the NSAID comparators.

[Slide.]

Turning now to the study design, the CLASS study was double-blind, randomized, parallel group study that was separated into two protocols that were performed contemporaneously, which were identical save for the comparator employed. They were designed to be analyzed in a pooled fashion. All patients were to be allowed an opportunity to participate for at least six months.

The inclusion and exclusion criteria were constructed in a way to replicate clinical practice. Accordingly, patients who had a clinical diagnosis of either OA or RA could be enrolled and were only excluded if they

presented a contraindication for the use of the study drugs, specifically a history of recent or active GI disease or any other comorbidities, such as serious renal or hepatic disease.

[Slide.]

In keeping with this being a real world study, low dose aspirin use was permitted. Again, cardiovascular disease is common in the arthritis patient population. In addition, patients were allowed to use antacids on a limited basis, predominantly calcium supplements for osteoporosis.

They were prohibited, however, from using any anti-ulcer drugs, either H2 receptor antagonists or proton pump inhibitors because of their propensity to either mask symptoms or alter the outcomes of interest. In addition, patients were also not allowed to take NSAIDs during the trial.

The treatments employed were celecoxib at the dose of 400 mg twice daily, again, 2 times the RA dose and 4 times the OA dose, which were maximally effective, and the doses of the comparators were 75 mg twice daily of diclofenac, a commonly used dose for the indications in the trial, and ibuprofen, 800 mg three times daily, again a commonly used dose of ibuprofen for OA and RA.

[Slide.]

The trial power calculation was based on ulcer

complication rates of 0.3 events per 100 patient years for celecoxib and 1.2 events per 100 patient years for NSAIDs.

Additional assumptions were that these incidence rates would remain constant over time and that aspirin use would approximate that seen within the context of the NDA, approximately 12 percent.

The trial was powered to include a total of 40 events, requiring the enrollment of 8,000 patients, 4,000 on celecoxib and 4,000 on the NSAIDs, 2,000 per each comparator.

[Slide.]

In terms of the analysis plan, the endpoints to be analyzed were ulcer complications, as well as symptomatic ulcers and ulcer complications. The statistics were based on an intent-to-treat analysis and included all patients who took at least one dose of study medication.

The principal statistical test was the log-rank test of time-to-event, and a step-wise comparison was planned in which celecoxib was compared to the NSAIDs combined and then to each NSAID separately.

[Slide.]

Risk factors prespecified in the protocol included aspirin use, as well as the risk factors defined by the previously performed MUCOSA trial, as well as a variety of other risk factors which Dr. Geis discussed.

[Slide.]

There were three oversight committees which supervised the performance of the trial.

[Slide.]

The committees and their membership are shown in this slide. They consisted of the GI Events Committee chaired by Dr. Goldstein and his colleagues, the Data Safety Monitoring Board chaired by Dr. Faich and his colleagues, and the Executive Committee chaired by Dr. Silverstein and his colleagues.

[Slide.]

Their charters are simplified in this slide. In brief, the GI Events Committee was to review all potential GI events reported during the conduct of the trial.

The Data Safety Monitoring Board monitored the accrual of such events and in addition performed the safety oversight function looking at general safety during the execution of the trial.

The Executive Committee was the main oversight body and administered study conduct.

[Slide.]

I would like to review for you in some detail now how information was funneled into the GI Events Committee and then judged by the committee.

Investigators were asked to monitor for the signs

or symptoms of ulcer complications, which included but were not limited to such symptoms and signs as dyspepsia, abdominal pain, the presence of anemia or melena.

If any were present, they were asked to evaluate the patient according to their ordinary clinical care patterns, but they were required or asked to obtain at a minimum stool testing for occult blood, hematocrit and hemoglobin, as well as perform vital signs for determination of volume status, and if indicated, they were to perform an endoscopy or contrast radiographic study.

Clinical care was dictated as appropriate for the work-up and the results obtained.

[Slide.]

All the information obtained by the investigators was reported to the GEC or GI Events Committee.

[Slide.]

The GI Events Committee reviewed all such reports and either diagnosed them as an ulcer complication, a symptomatic ulcer, or assigned to them some other diagnosis other than those two.

[Slide.]

Ulcer complications were prospectively defined in the protocol as either bleeding ulcers, perforated ulcers, or ulcers causing gastric outlet obstruction, and in this trial, all ulcer complications required hard documentation,

that is, endoscopic or radiographic proof of an evidence of an ulcer or a large erosion.

[Slide.]

Upper GI bleeding ulcers were the most common complication and were subcategorized into four categories again as prespecified by the protocol. Each category required the presence of a lesion.

There was either hematemesis with the lesion or the lesion demonstrated either active bleeding or evidence of recent bleeding, the presence of melena with the lesion, or the presence of blood in the stool by hemoccult testing along with some clinical evidence of substantial blood loss.

[Slide.]

Symptomatic ulcers were also defined in the protocol as any mucosal break with unequivocal depth found on a "for cause" work-up, that is, a work-up performed to investigate either a sign or a symptom of a potential ulcer complication. Again, all ulcer complications required hard documentation, that is, either endoscopic or radiographic documentation.

[Slide.]

I would like now to share with you the results of the trial, and I would like to direct my remarks first to GI outcomes and then to general safety outcomes.

In discussing with you the GI outcomes, I would

first like to describe the study population, the GI outcomes, and then potential sources of bias that may arise in assessing ulcer complications.

After discussions with the agency, we will focus today's discussion entirely on the entire study results as opposed to the six-month analyses that have been presented in the briefing documents.

[Slide.]

The demographics of the study population are shown here. Patients averaged 60 years in age and were predominantly female with the ethnic distribution as shown. Seventy percent of the patients had a primary diagnosis of OA and 30 percent a primary diagnosis of RA. No differences were seen between the treatment groups.

[Slide.]

In terms of the risk factors as defined by the MUCOSA trial, approximately 11 to 12 percent of patients were either 75 years or older, 1.5 percent had a prior history of GI bleed, and approximately 8 percent had a prior history of ulcer disease. Forty percent of the patients had a history of cardiovascular disease, again reinforcing my comment that cardiovascular disease is a common comorbidity in the arthritis patient population. No differences between treatment groups were observed.

[Slide.]

Aspirin was used by approximately 22 percent of the trial population, steroids were used by approximately 30 percent of the trial population, and anticoagulants, which were permitted, were used by approximately 1 percent of the trial population. No differences between treatment groups again were apparent.

Although over-the-counter NSAIDs were prohibited during the trial, approximately 5 to 6 percent of patients in each of the treatment groups used such over-the-counter NSAIDs, and in keeping with this being a real world clinical trial, such patients were not removed from the protocol, but were analyzed and kept within the study.

[Slide.]

Patients participated for a mean of approximately 7 months with a maximum exposure ranging between 12 and 15 months. Total exposure in the trial approximated 4,500 patient years split equally between celecoxib and the two NSAID comparators.

[Slide.]

I would like to characterize for you individually now the demographics of both the OA, as well as the RA cohort contained within this trial. OT patients on average tended to be slightly older than the overall study population and were predominantly female. These patients had long-standing OA of approximately 10 years in duration

and most had been on prior NSAID therapy up until the inception of the trial. Again there were no differences between treatment arms.

[Slide.]

The RA population within the trial tended to be younger, was still predominantly female, but had long-standing disease of approximately 10 years in duration. Most had used NSAIDs prior to the trial, and approximately 50 percent used steroids and/or methotrexate during the trial, and again there were no differences between treatment arms.

[Slide.]

In terms of the disposition of patients, approximately 50 percent or actually slightly less than 50 percent of patients completed the trial. Significantly, fewer patients assigned to the ibuprofen arm completed the trial compared to celecoxib patients.

More patients on diclofenac withdrew for adverse events compared to the celecoxib-treated patients, and more patients withdrew from the trial for treatment failure assigned to ibuprofen relative to celecoxib. No patients were lost to follow up that is, their medical status was ascertained at the time they exited from the trial, so no information is lacking because of lost to follow up patients.

[Slide.]

So, to summarize, this was a representative cohort of arthritis patients. Aspirin use was substantial, approximately 1 in 5 patients used aspirin. No information was lost because of lost to follow up patients.

Exposure to the study drugs was substantial and ranged up to 15 months. Moreover, there was a higher incidence of withdrawals seen from the study compared to celecoxib, in ibuprofen-treated patients for treatment failure, and diclofenac-treated patients for adverse events.

I would like now to discuss for you the GI outcomes of the trial.

[Slide.]

During the trial, 1,500 cases of potential ulcer complications were reported and each was evaluated by the committee. Forty-four of these cases were diagnosed as ulcer complications, 67 as symptomatic ulcers which did not meet the definition of ulcer complication, and the balance were assigned other diagnoses.

[Slide.]

In terms of the incidence of ulcer complications, there was no difference in comparing celecoxib to the NSAIDs combined as a group.

[Slide.]

In terms of the combined endpoint or the extended

endpoint, symptomatic ulcers and ulcer complications, there was a significant difference observed between NSAIDs and celecoxib with approximately a 40 percent reduction with a p-value as shown.

[Slide.]

The Kaplan Meier curves which form the basis of the prior bar graph are shown here. Again, there was a linear accrual of events throughout the duration of the trial with a p-value as shown here. This p-value is obtained from the log-rank test of the time-to-event.

[Slide.]

Because the comparison with NSAIDs was significant, we next compared with the individual comparators. There was no significant difference between celecoxib and diclofenac, but there was an approximately 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications associated with celecoxib compared to ibuprofen with a p-value as shown.

[Slide.]

The Kaplan Meier analysis of this bar graph is shown here. Again, events accrued in a linear fashion throughout the trial in both treatment arms with the treatment difference being relatively easily apparent with a p-value of 0.017.

[Slide.]

So, in sum, comparing celecoxib to NSAIDs as a group, there was a lower incidence of symptomatic ulcers and ulcer complications associated with celecoxib, and this was also specifically true of the comparison of celecoxib to ibuprofen.

[Slide.]

I would like to turn now to consideration of the risk factors for such events.

[Slide.]

The prespecified risk factors are shown here and are related either to the patients' characteristics, their underlying disease, their concomitant medications, or prior medical history.

[Slide.]

Risk factors which were significant in terms of being associated with the outcome are symptomatic ulcers and ulcer complication were age greater than or equal to 75 years, a prior history of ulcer disease or upper GI bleeding, and cardiovascular disease.

Cardiovascular disease was a risk factor only by virtue of its association with aspirin use. In addition, aspirin use was shown to have a significant effect on treatment outcome.

[Slide.]

Risk factors which were not significant are shown

here and included gender, alcohol or tobacco use, or disease type or duration, or steroid use.

[Slide.]

So, this trial actually confirms the MUCOSA study risk factor analysis, and additionally indicates that aspirin use has an important effect on treatment outcome.

[Slide.]

Accordingly, we next analyzed the effect of aspirin use by examining the outcomes in both the aspirin-treated patients and the non-aspirin-treated patients.

[Slide.]

As shown here, there was no difference in the incidence of symptomatic ulcers and ulcer complications in patients on aspirin with the p-value as shown. There was, however, a 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications in patients on celecoxib as compared to NSAIDs combined with a p-value of 0.02.

[Slide.]

Turning now specifically to the comparison of ibuprofen to celecoxib, there was no difference in the incidence symptomatic ulcers combined with ulcer complications in aspirin users, but there was an approximately 2- to 3-fold reduction in non-aspirin users, this value being significant with a p-value of less than 0.001.

[Slide.]

This Kaplan Meier curve shows the analysis of the non-aspirin users comparing celecoxib to ibuprofen. Again, events accrued linearly with time over the course of the trial, and the treatment difference is readily apparent with a p-value based on the log-rank test as shown.

[Slide.]

The profound effect of aspirin in terms of the analysis of GI outcomes is shown in this graph. If one looks at the primary outcome, that is, ulcer complications, and compares celecoxib to ibuprofen, there is a 2- to 3-fold reduction in the incidence of such comparing the two treatment arms, the p-value for this comparison being 0.037.

[Slide.]

So, in conclusion, among non-aspirin users, there is a lower incidence of symptomatic ulcers and ulcer complications in patients on celecoxib compared to those on NSAIDs and ibuprofen specifically, whereas, there is no difference apparent within the context of aspirin use.

[Slide.]

Part of the robustness of this trial is that it allows us to look at both RA and OA separately, and this is a question, of course, which is of interest to practitioners, that is, how do these drugs perform in these different patient populations.

[Slide.]

In separating out the results for RA and OA, comparing NSAIDs to celecoxib, two conclusions can be drawn here. One is that the overall rates for each of the treatment arms is similar between the two arthritides.

Additionally, the treatment effect within each type of arthritis is similar. This was statistically significant within the context of RA with a p-value of 0.04 and approached statistical significance within the context of OA.

[Slide.]

We can also look at this comparison within the context of patients not using aspirin. As shown here, in RA patients not using aspirin, there is an approximately 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications, this value being significant, and an approximately 2-fold reduction in OA, this p-value approaching significance.

Again the incidence of ulcer complications and symptomatic ulcers between the two types of arthritis is relatively similar.

[Slide.]

Turning now to a specific comparison between celecoxib and ibuprofen, one sees similar results. The OA and RA results for symptomatic ulcers and ulcer

complications for each of the treatment arms is quite similar between the two different types of arthritis, and the treatment differences or treatment effects are similar. This approached statistically significance within the OA cohort with a p-value of 0.11, and was significant within the RA cohort with a p-value of 0.017.

[Slide.]

Among non-aspirin users, there was a 2- to 3-fold reduction in the incidence of symptomatic ulcers and ulcer complications in OA patients with a p-value as shown, and a 3- to 4-fold reduction in the context of RA with a p-value as shown.

[Slide.]

This last bar graph is shown as a Kaplan Meier analysis. Here again, for the non-aspirin cohort of RA patients, as you can see here, events accrued literally over time during the trial, and the treatment effect is readily apparent with a p-value of less than 0.001.

[Slide.]

So, in sum, in comparing OA to RA, the incidence of symptomatic ulcers and ulcer complications is similar between the two types of arthritis. Moreover, the treatment differences between celecoxib and NSAIDs, or celecoxib and ibuprofen, are similar in the two types of arthritis.

[Slide.]

This trial taught us a lot about outcome trials and potential sources of bias in assessing the endpoint of ulcer complication.

[Slide.]

One such source of bias was the use of low dose aspirin, and that I have outlined for you in detail previously. Another potential source of bias that can enter into such trials with respect to determining the rate of ulcer complication is the withdrawal of patients with symptomatic ulcers.

[Slide.]

Now, GI outcome trials, such as CLASS, assumed that after treatment initiation, the patients would go on to develop an ulcer complication and be withdrawn from the trial as an event.

[Slide.]

However, if patients develop an earlier form of the disease, which can be found by investigators, and identified, leading to their removal from the trial, they will lower the rate of ulcer complications observed.

Now, this source of bias will only be important if there is differential withdrawal for symptomatic ulcers between treatment arms, and as you can see in the next graph, withdrawal for symptomatic ulcers alone was significantly greater among patients treated with NSAIDs

than celecoxib. This differential withdrawal then can introduce bias in the assessment of ulcer complication incidence.

[Slide.]

So, in sum, celecoxib is associated with lower incidence of symptomatic ulcers alone compared to NSAIDs, and the withdrawals for such may bias the analysis of ulcer complications in a trial such as this.

[Slide.]

I would like to turn now to consideration of general safety and summarize my comments into either a consideration of overall safety, an analysis of safety specifically focused on the four body systems shown here, an analysis in aspirin users, and an analysis of patients of all ages particularly focusing on patients who are over 65 years of age.

[Slide.]

In terms of overall safety, deaths occurred uncommonly during the trial and were large due to cardiovascular disease because cardiovascular disease is a common cause of morbidity and mortality in this patient population.

Serious adverse events, those leading to hospitalizations, occurred in approximately 10 cases per 100 patient years of exposure. There were no differences

between treatment groups either in deaths or serious adverse events.

That was also specifically true of cardiac serious adverse events or all-cause GI serious adverse events, which includes a large subset of events not restricted to the outcomes of the trial, such as esophageal, colonic, or pancreatic serious adverse events.

There were no serious dermatologic adverse events noted in patients assigned to celecoxib, and they occurred infrequently among the other treatment arms. Renal serious adverse events were also rare and consisted largely of renal calculi.

[Slide.]

The common adverse events which occurred during the trial are shown in the following two slides.

Common adverse events were significantly more common in patients assigned to diclofenac than to celecoxib, principally for those related to the GI system - dyspepsia, abdominal pain, diarrhea, nausea shown here.

[Slide.]

Rash was more common among patients assigned to the celecoxib-treated arm, but anemia, and peripheral edema were more common among patients assigned to the ibuprofen-treated relative to celecoxib.

Again, constipation as a GI side effect was more

frequently seen in patients assigned to diclofenac, and elevated transaminases in specific ALT was seen more frequently in patients assigned to diclofenac.

[Slide.]

Adverse events causing withdrawal were significantly more common in patients assigned to diclofenac compared to celecoxib. This difference was largely driven by withdrawals due to GI events, such as abdominal pain and nausea or, or hepatic events, such as elevated transaminases as shown here.

[Slide.]

So, in summary, celecoxib appeared to be well tolerated at this super-therapeutic dose as compared to the NDA database that has been reviewed previously. In addition, no dose- or duration-related increases in adverse events were seen with the exception of non-serious rash during the course of the course of the CLASS trial.

[Slide.]

I would like to now focus on the GI system. In terms of GI adverse events, any cause adverse event was significantly more common in patients assigned to diclofenac compared to celecoxib, and this difference was largely driven by the common GI adverse events shown here - dyspepsia, abdominal pain, nausea, diarrhea and constipation.

The clinical relevance of this difference in tolerability is shown by the significant difference in withdrawals. Withdrawals were significantly more common in patients assigned to diclofenac as compared to those assigned to celecoxib.

[Slide.]

The protocol also prespecified a definition of what was considered to be a clinically significant decrease in hematocrit or hemoglobin. Any decrease in hematocrit of greater than or equal to 10 percentage points, or hemoglobin greater than 2 grams per deciliter, was defined as being clinically significant.

In terms of the incidence of such decreases, they were significantly more frequent on both treatment arms as compared to patients assigned to celecoxib, that is, they are more frequent among NSAID-treated patients.

This was not simply a function of overt bleeding due to ulcer bleeds because if you remove patients with ulcer bleeds from the analysis, the incidence of such significant changes in hematocrit and hemoglobin were still significantly more common in patient on NSAIDs as compared to patients on celecoxib.

[Slide.]

These decreases in hematocrit and hemoglobin were associated with decreases in iron stores as indicated by the

iron/iron binding capacity. As shown here, these ratios tended to decrease in diclofenac- and ibuprofen-treated patients relative to patients on celecoxib.

[Slide.]

So, in conclusion, celecoxib appeared to be associated with a lower incidence of GI adverse events and withdrawals for such relative to diclofenac, and a lower incidence of clinically significant reductions in hematocrit and hemoglobin relative to both NSAID comparators.

Moreover, the decrease in iron stores that were associated with such decreases suggests and are consistent with chronic GI blood loss occurring with the NSAID comparators.

[Slide.]

In terms of renal adverse events, overall renal adverse events were significantly more common in patients assigned to ibuprofen compared to celecoxib. This difference was attributable to a significantly higher rate of hypertension, generalized or peripheral edema in patients on ibuprofen.

[Slide.]

Also, in the protocol, there was predefined definition of clinically significant renal lab abnormalities. That consisted of any patient who exhibited serum or urea nitrogen or BUN of greater than or equal to 40

mg percent, or a creatinine greater than or equal to 1.8 mg percent.

Such clinically significant abnormalities were significantly more common in patients assigned to diclofenac as compared to patients assigned to celecoxib.

[Slide.]

So, in sum, celecoxib appeared to be associated with a lower incidence of hypertension and edema compared to ibuprofen, and a lower incidence of clinically significant increases in creatinine and/or BUN than diclofenac.

[Slide.]

In terms of hepatic issues, this graph show the protocol-defined clinically significant elevations in hepatic transaminases, those that were 3 times the upper limit of normal.

Such elevations occurred in approximately 3 1/2 percent of patients treated with diclofenac consistent with the known hepatotoxic potential of diclofenac. This was significantly and substantially greater than the rates seen in patients assigned to celecoxib.

Withdrawals for such transaminase elevations were commensurate, that is, approximately 3 1/2 percent of patients withdrew from the trial for such elevations in patients assigned to diclofenac, and that was commensurately reduced in the patients assigned to celecoxib.

[Slide.]

So, celecoxib was clearly associated with a lower incidence of clinically significant increases in transaminases relative to patients assigned to diclofenac.

[Slide.]

Turning to the cardiovascular system, thromboembolic events in the trial were seen with equal frequency on all three treatment arms. That was true for any arterial or venous thromboembolic event or specifically true for the four major cardiac thromboembolic events - MI, angina, coronary artery disease, or unstable angina.

Stroke actually was seen significantly less commonly among patients assigned to celecoxib compared to those assigned to ibuprofen.

[Slide.]

Now, in consideration of patients not treated with aspirin, of course, is important because these represent patients potentially at risk for such complications, however, no treatment differences were observed between the treatment arms in the CLASS study even among this cohort for any thromboembolic event or specifically for MI, angina, CAD, or unstable angina.

Stroke again was significantly less common in patients assigned to celecoxib relative to diclofenac.

[Slide.]

Atrial dysrhythmias are shown in this slide. Atrial fibrillation was the most common atrial dysrhythmia observed in this patient population, again consistent with this being an older patient population. No treatment differences were observed for this arrhythmia or any of the other atrial arrhythmias observed or shown eh re.

Congestive heart failure was rare during the trial and it occurred with equal frequency in all three treatment arms.

[Slide.]

Looking specifically again at patients not treated with aspirin, the incidence of atrial fibrillation was low and not different between treatment arms, and other atrial dysrhythmias were rare.

Congestive heart failure also was rare within the study, and not different between all three treatment arms, but withdrawals for congestive heart failure were significantly more common in patients treated with ibuprofen compared to patients treated with celecoxib.

[Slide.]

So, overall, comparing celecoxib to both the NSAID comparators, there was no difference in thromboembolic events observed and no difference in the incidence of atrial dysrhythmias or congestive heart failure.

The GI protective effect in terms of the GI

outcomes of the trial were predominantly seen within the context of non-aspirin users. It is an important issue for clinicians and an important aspect of this trial to analyze what the safety profile is in the context of aspirin use.

[Slide.]

As shown here, selectively in aspirin users, any GI adverse event and withdrawals for such were more common among patients treated with diclofenac compared to those with celecoxib, this difference being significant for withdrawals.

Renal events again were significantly more common in patients treated with ibuprofen relative to celecoxib. Again this is within the aspirin using population.

[Slide.]

Although aspirin increased the incidence of clinically significant changes in hematocrit and hemoglobin in all three treatment arms, the treatment differences were preserved, that is, there were fewer such decreases in patients treated with celecoxib as compared to those treated with either diclofenac or ibuprofen.

[Slide.]

In terms of clinically significant renal abnormalities, that is, increases in renal function tests, they tended to be higher among aspirin users consistent with this patient population having a higher incidence of

cardiovascular disease, but the treatment difference between diclofenac and celecoxib was preserved and was significantly different between these two treatment arms.

[Slide.]

Hepatotoxicity was evident regardless of the use of aspirin, and the treatment differences between diclofenac and ibuprofen were preserved and substantial.

[Slide.]

So, in sum, even among aspirin users, the general safety profile is quite similar to the patients not on aspirin with respect to GI, renal, and hepatic safety.

[Slide.]

It is particularly important to look at safety within the context of the older patient, because the arthritis patient population tends to be older, and this slide summarizes for you in very brief form the safety in patients who are 65 years or older.

[Slide.]

GI adverse events again occurred significantly more commonly in patients assigned to diclofenac. Decreases in hematocrit and hemoglobin were also significantly more common in patients assigned to either of the two NSAIDs comparators compared to diclofenac.

Overall renal adverse events were significantly more common again in patients treated with ibuprofen, and

increases in renal function tests were significantly more common in patients treated with diclofenac. Hepatotoxicity was even more apparent within this older patient population, and again, there was a significant and substantial difference between patients treated with diclofenac and celecoxib.

[Slide.]

So, the safety profile of celecoxib appears to be maintained even within the older population.

The following two slides will then summarize all the comments that I have made in graphical form.

[Slide.]

The GI safety advantages of celecoxib, which are largely mechanism, that is, COX-2 based, are shown here. Celecoxib was associated with a significantly decreased incidence of symptomatic ulcers and ulcer complications versus NSAIDs combined and ibuprofen specifically.

Celecoxib was associated with less chronic GI blood loss versus NSAIDs combined or either of the two comparators, and associated with fewer GI adverse events versus both NSAIDs combined and diclofenac specifically.

Blood loss and tolerability differences were also evident within aspirin-using patients.

[Slide.]

In terms of general safety attributes, which may

be largely molecularly based, not mechanism based, celecoxib was associated with less edema and hypertension compared to ibuprofen, and fewer increases in creatinine and BUN compared to diclofenac, and again, less hepatotoxicity compared to diclofenac, these results being similar in the aspirin-using patient population.

Moreover, the safety profile appears to be similar in all age groups, and the CLASS trial does not substantiate that celecoxib is associated with an increased risk of cardiac or thromboembolic events.

Thank you.

I would like to now turn over the podium to Dr. Fred Silverstein who is the Chair of the Executive Committee for the CLASS trial to make some concluding remarks.

Summary

DR. SILVERSTEIN: Thank you very much, Dr. Lefkowith. Those really were three outstanding presentations.

I sit here, stand here as a clinical investigator who has worked in the field of GI bleeding for almost 30 years, and I am absolutely astounded by how much more we know now about why people bleed and who is bleeding than we knew when I started.

In 1974, I was asked by the head of the School of Biomedical Engineering at the University of Washington to

develop methods to control bleeding using lasers and heated monopolar and a variety of techniques.

I spent about a decade of my life doing that with Dr. David Auth, but then I realized in the early eighties that I didn't really know who was bleeding, and so we did a large study with the ASGE looking at the demographics of what patients were bleeding.

It was just at this time that this association with NSAIDs was becoming clear and then I got involved in understanding that and in looking at protective agents and specifically prostaglandins. Then, we did the MUCOSA trial, which kind of put these things together a big, and then I was privileged to be able to work with the COX-2 inhibitors, but I am telling you we know so much more now than we did in 1963, when I started in medical school about what causes ulcers.

Almost everything we thought then was wrong, what caused them, how to diagnose them, what to do about them, and things have really progressed with the H. pylori hypothesis and with the understanding of the importance of nonsteroidal agents. So, I think it has just been a truly remarkable advance in our knowledge, and I think the advantages of the COX-2 inhibitors are really pretty apparent.

Could I have Slide 1141, please.

[Slide.]

So, I would just like to briefly summarize what I take away from what I just heard as a consultant clinical investigator from Seattle to Searle.

The first has to do with the trial design. This was a truly rigorously designed trial. It was blinded. I chair the Executive Committee. I guarantee the blind was never broken, not once. We had no idea what groups patients were in or what medication the patients were on.

It was a randomized, blinded trial, and really the people who deserve the most credit are the patients who donated all of their effort to being part of the trial, along with the physicians, the nurses, the clinical research associates, et cetera, but I think it was a remarkable effort, and it has resulted in a huge database of very robust data, and I think the agency's analysis of the study agrees with that, that this is a very well done study with some really good data that we can use.

Of interest to me, we designed the study using the safest NSAIDs as comparators with ibuprofen and diclofenac at doses of celecoxib which were higher than at 2X or 4X, the approved dose of celecoxib for the intended population, whereas, the NSAIDs were used at the routine dose.

We didn't allow proton pump inhibitors or H2 blockers which might have masked symptoms, and kept people

in the trial until they developed a complication as opposed to saying, hey, she is symptomatic, she was endoscoped, she had an ulcer, she is coming off the trial before she developed a complication.

And we allowed aspirin, which I think is critical because you have already seen that it has a dramatic effect, and I think it is an important part of a study of this type.

So, I think it is an excellent trial design.

To look at the clinical results of the trial, I would like to turn to Slide 257, please.

[Slide.]

So, what was presented here was the ulcer complication rate in all the patients, had a trend in the right direction, but was not quite statistically significant. When the patients who were taking aspirin were taken out of the analysis, the change was more apparent.

What I am going to address in the next just few minutes is what happened, you know, what happened to the way we planned the trial versus the way the trial turned out, and one of the key things is that nothing happened to the celecoxib group.

The celecoxib group basically did what it was predicted to do. It had, off of aspirin, it had about a 0.4 percent complication rate. That wasn't the issue. The issue was why did the comparator nonsteroidals have a lower

rate, which is what created this question about why the primary endpoint wasn't quite achieved.

Could I have 256, please.

[Slide.]

So, when we look at the primary endpoint was this ulcer complication endpoint, and then as you heard in Dr. Lefkowith's presentation, the symptomatic ulcers were added to that. This was an endpoint, a secondary endpoint, which was identified prospectively in the protocol, and it seems to me to make sense to combine them.

Now, Dr. Geis, in that lovely tutorial on ulcers and NSAIDs, showed us that the difference between a complicated ulcer. So, when we combined the symptomatic ulcer, the question is should we be looking at a meaningful endpoint of combining the symptomatic ulcers, and from my clinical standpoint, I would say absolutely we should.

Steve showed us that the difference. I have endoscoped thousands of patients and hundreds, as many of you have, of bleeding patients, and the difference between a patient who has a ulcer and a patient who has a bleeding ulcer, a complicated ulcer, is really a temporal phenomenon in some cases, and I think it does make sense from a clinical standpoint to combine those two as another endpoint, an alternative endpoint.

Now, could I have Slide 124, please.

[Slide.]

Now, the question then is, well, what happened. I mean this was an evidence-based trial in terms of design. We took this huge amount of data from the MUCOSA trial, from the literature, et cetera, and designed the trial.

The question was, well, what happened. Well, things happen, and what happened was that there were changes in several aspects of the way patients were entered into the trial and managed on the trial.

What do I mean? Well, in the MUCOSA trial, as Dr. Lefkowith pointed out, we identified four risk factors as being important for increased likelihood of a complication, and you can see the incidence of each of those factors.

But look what happened in the CLASS trial. They went down. There were fewer people with these risk factors entered in the CLASS trial, and that just reflects clinical practice. Practitioners are smart, they read the literature, they know these people are at risk, and they tend to change the nature of the people they will put on a clinical trial.

So, the first factor was that there was a change in the underlying risk of the patients in the CLASS trial, which had not been prospectively anticipated.

May we have 126, please.

[Slide.]

Now, the second factor was the use of aspirin, and here I am comparing the NDA database in which 12 percent of people were on aspirin, as I believe Steve mentioned earlier, and in the CLASS trial, where 22 percent of patients were on aspirin, and this probably, once again, reflects changes in clinical practice, more people in the older population being put on aspirin prophylaxis. Whether that is the right thing to do or not for primary prophylaxis is yet another issue.

But clearly, again, the CLASS trial had this factor, which was almost twice as large numerically as the NDA data, and as we have seen from the data that Dr. Lefkowith showed us, had a very significant impact on outcome.

Can we have 126, please.

[Slide.]

The third factor I want to show you, of multiple factors we could talk about, has to do with how many patients were worked up from a GI standpoint.

In the MUCOSA trial, which was a huge body of work, about 2.7 percent of people were worked up for abdominal symptoms to determine if they had an ulcer, et cetera, but in the CLASS trial, this almost doubled to 4.8 percent.

Now, what that means clinically is that patients

were presenting with symptoms, they were being endoscoped for cause, and if they had an ulcer, they were being taken off the trial as a symptomatic ulcer, and for the reasons that Steve showed you, I believe, as he does, that ulcers become complicated ulcers. If you take an ulcer out of the trial, that ulcer cannot become a complicated ulcer. So, that is another change that occurred that could not have been discerned from the MUCOSA trial, but did occur in the CLASS trial.

122, please.

[Slide.]

The final slide is looking at the data using the combined endpoints saying ulcer complications are important, we told you what happened with that, but symptomatic ulcers are important, too, and when you combine then and you look at all patients, you see the difference that occurred with celecoxib, and especially when you take the aspirin patients out, you see an even more remarkable difference in the reduction from NSAIDs to celecoxib for the combined endpoint.

Once again this is what we expected. We did expect this type of data with celecoxib. It was rather the comparators that were the issue.

So, can we go back, please, to Slide 1141.

[Slide.]

And so in conclusion, I would say that there is a large body of data about celecoxib and the GI tract. There are about 60 controlled trials in about 25,000 patients. There is a large body of data that I think suggests that there is improved GI safety in terms of GI symptoms, withdrawal for GI symptoms, complications symptomatic ulcers, et cetera.

I think that, therefore, the CLASS trial actually confirmed the antecedent trials with the notes that I made about why there were some differences.

The safety data from the CLASS trial, which is also a large body of data, also found no new signals. There was not evidence of cardiovascular or renal effects, and it looks as if celecoxib is not any worse than NSAIDs, and in some ways may be somewhat better.

So, again, we have expanded this large safety database, and we are not finding any signals of unanticipated adverse events.

[Slide.]

So, in conclusion the NSAID problem is a large problem. The gastroenterologists and the rheumatologists didn't agree about this for a couple of decades because they were saying, hey, it's only 1 percent, I have 300 in my panel, and only seen one or two events a year.

The gastroenterologists were saying that is crazy,

half the people I see coming in bleeding are on NSAIDs.

So that has become resolved as we have understood these numbers, but if there are 15 or 17 million people on NSAIDs in the United States, and a 1 percent incidence of that is 150,000 to 170,000, it is a lot of people, and if we can cut that in half, then, you have saved 50- or 100,000 of these bleeding episodes.

So, even though the incidence is small, because of the population exposed is so large, it is a major problem. So, what I would include is that the data from the CLASS trial supports the fact that celecoxib is a safe and effective drug and is well tolerated, and I think is a real addition to our armamentaria for patients with arthritis.

Thank you.

DR. HARRIS: Thank you very much, Dr. Silverstein.

I am going to just ask now if there are any questions of clarity that one may want to ask any of the sponsors by any member of the committee? Yes.

DR. PINA: I have a whole series of questions actually.

Of the whole 40 patients that had a cardiovascular history, how many of those were the aspirin users? You have 22 percent on aspirin at entry and 40 percent of patients with a cardiovascular history, are the 22 percent part of that 40 percent?

DR. LEFKOWITH: In using the guidelines, the FDA guidelines for what is appropriate secondary prophylaxis, approximately, 16 percent of the patients, that is 16 percent, not of the 22 percent, but 16 percent were taking it for secondary prophylaxis and 6 percent were taking it for other reasons.

DR. PINA: But were those part of the 40 percent that had the cardiovascular history at entry?

DR. LEFKOWITH: Cardiovascular disease was defined as any instance of cardiovascular disease. All patients given it for secondary prophylaxis would have met that definition of cardiovascular disease.

DR. PINA: I have another question if I may. You don't talk about other concomitant use of drugs, and if you have such a high number of patients with cardiovascular disorders, I would think that among them, and many of them hypertensives, there is a high use of ACE inhibitors in this group.

Did you set aside the ACE inhibitor patients, do you know how many patients were on ACE?

DR. GEIS: As part of the normal course of the study, we did collect concomitant medications, and we can provide you that data.

DR. LEFKOWITH: In terms of the use of ACE inhibitors specifically, in incidence of patients who

entered the trial using ACE inhibitors is shown here. The incidence of those starting ACE inhibitors during the trial is shown here.

Does that answer your question?

DR. PINA: Well, it answers my question as far as entry drug criteria, but I again start wondering about the interactions of these drugs with patients on these inhibitors, particularly with the renal effects, and I am sure we will get to this a little bit later.

DR. HARRIS: Dr. Wolfe?

DR. M. WOLFE: I had a similar question. I was really surprised at the number of patients on ibuprofen, taking ibuprofen over the counter, as well, as well as naproxen over the counter, and even though they were instructed not to take H2 blockers or PPI's, were they taking it either in prescription form or over the counter?

DR. GEIS: We can present that data. Dr. Lefkowith.

DR. LEFKOWITH: Prescription or over-the-counter H2 blockers or PPI's?

DR. M. WOLFE: Prescription PPI's.

DR. LEFKOWITH: Prescription PPI's.

DR. M. WOLFE: Over the counter or prescription, both.

[Slide.]

DR. LEFKOWITH: This is for NSAID use. You were asking for PPI's or H2 blockers? I am sorry. You wanted the PPI's and the H2 blockers. We will get that up in a second.

Such use obviously did occur during the trial, and patients were not excluded if they used it over the counter. Prolonged use that was discovered during the trial of PPI use or at prescription doses, however, did lead to patients being removed from the trial as a protocol violation.

Could we have the slide, please.

[Slide.]

As you can see, this is an overwhelming list of medications which taxes my visual acuity at this distance, but maybe we can cone down in terms of H2 receptor antagonists, the use was approximately 5 percent in the trial population. I don't believe we show here any use of PPI's. PPI's were used predominantly in the treatment of events, but H2 receptor antagonists were used during the trial by the patient population.

DR. HARRIS: Yes.

DR. WOFSY: I also have two questions relating to thrombotic events, one in aspirin users and one in non-aspirin users.

What was the thrombotic event rate in the aspirin users? It seems that we had a lot in the non-aspirin users.

Do you have any data on the cardiovascular thrombotic event rate in aspirin users compared to non-aspirin users?

DR. GEIS: Yes, we do. We can pull that slide.

DR. LEFKOWITH: Could we have the slide, please.

Now, the incidence of thromboembolic events in the aspirin users is higher than non-aspirin users, which I showed you during my talk. It's about 5 percent. That is because, of course, the patients using aspirin are at risk for cardiovascular events, that is why they are on aspirin, but there were no treatment differences observed between celecoxib and the NSAIDs for either any thromboembolic event or the specific cardiac thromboembolic events that I showed you or for stroke.

DR. WOFSY: And in non-aspirin users, the question really has to do with statistical power. If I recall your slide correctly, there was an increase that was not statistically significant in the patients who were treated with Celebrex.

Would you have been powered, at what level were you powered to detect a statistically significant difference in that area?

DR. GEIS: I would like to have Dr. Jerry Faich, the head of our DSMB, respond to that question.

DR. FAICH: The short answer is that study was not powered to detect such a difference. Later on perhaps we

can talk about--the best way to go at that, this is a study of 2,000 person years of exposure to celecoxib, is to look at a pooled analysis including the NDA and the open label extension. Perhaps this afternoon would be a better time to do it, but the short answer is there isn't a powered answer to that question, but there wasn't a signal, I mean, so it goes both ways.

DR. HARRIS: Dr. Cryor.

DR. CRYOR: With respect to this 5 to 6 percent use of the over-the-counter NSAIDs, have you assessed how that OTC NSAID use impacted your observations with respect to ulcer complications or symptomatic ulcers?

DR. GEIS: Yes, we have. Dr. Lefkowith will take that.

DR. LEFKOWITH: We examined the profiles of all the patients with ulcer complications for use of over-the-counter NSAIDs just to understand the confounding effect that it might have. There were three actually complications in both the Celebrex-treated group, as well as the NSAID-treated group, who used NSAIDs or over-the-counter NSAIDs concomitantly.

Most of that use was sporadic and not temporally related to the event. One patient assigned to the celecoxib-treated arm was on salicylamide for a prolonged period of time, at a time that was immediately proximate to

the event, and could have been related to an event. This patient, however, was still included as a celecoxib event in the analysis that I showed you.

DR. HARRIS: Dr. Sampson.

DR. SAMPSON: I understand that you did a pooled analysis of the two different studies. It would be helpful to see two slides, if you would have it, the patient disposition and the adverse events causing withdrawal broken separately by the two studies with the two different Celebrex treatments, one for Study 035 and one for Study 102.

DR. GEIS: I believe we do have that data broken out by study. We can pull the slide, and we can show that.

DR. LEFKOWITH: You wanted patient disposition unblinded or blinded?

DR. SAMPSON: Your Slide No. 93 and the other one would be 132.

DR. LEFKOWITH: Can I have the slide, please. I am having trouble hearing you without the microphone.

[Slide.]

This is the disposition within the comparison between celecoxib and ibuprofen in terms of completers and withdrawals for adverse events, and I believe the next slide is the same comparison between diclofenac and ibuprofen within the trial, which again shows the same results as the

pooled results.

DR. SAMPSON: Do you have that, though, broken down by study?

DR. GEIS: This analysis shows the celecoxib pooled.

DR. SAMPSON: I want to see the celecoxib separate. I am sorry if I did not make that clear.

DR. GEIS: We don't have it broken out in a slide, but maybe this afternoon we can bring that back and we can show you that, but we can get that.

DR. SAMPSON: That would also be for Slide 132, which is adverse events causing withdrawals at a rate greater than 1 percent?

DR. GEIS: And you want the adverse events causing withdrawals by study with celecoxib separate in that study, not pooled.

DR. SAMPSON: That is correct. Thank you.

DR. GEIS: We can pull that this afternoon, as well.

DR. NISSEN: I would be interested in seeing the myocardial infarction rates by drug, not pooling the other NSAIDs, because ibuprofen, you know, these two drugs have differing effects on platelets, so I would like to see the celecoxib versus the other two agents compared with respect to the myocardial infarction rate.

DR. GEIS: So, MI rate, celecoxib pooled versus diclofenac, versus ibuprofen. Do we have that slide?

DR. LEFKOWITH: Can I have the slide, please.

This was the chart that I showed you, and I did show a vast amount of data during the talk, but this slide does have the MI rates broken out by treatment group. This is for all patients. Now, of course, this includes both aspirin users, as well as non-aspirin users.

DR. NISSEN: I meant in the non-aspirin users.

DR. LEFKOWITH: Okay. Could we have the next slide, please.

This, of course, is an important comparison because these patients are not protected by cardiovascular aspirin. That rate was no different and quite low in all three treatment arms.

DR. M. WOLFE: Along those lines, though, it is a difficult question, is there a study or a breakout of the patients with a previous history of an MI, who were not treated with aspirin, yet, were treated with the other three drugs?

DR. GEIS: So, the question is do we have it broken out by patients with cardiovascular disease, a history, who were not on aspirin, is that right?

DR. M. WOLFE: Yes.

DR. LEFKOWITH: Can I have the slide, please.

[Slide.]

So, in terms of MI's, again, now, you are talking about ever smaller cohorts within the trial, so you have to take these numbers in the context of being subanalysis, but nonetheless, if you look at MI's on celecoxib in patients not on aspirin, with a prior history of cardiac disease, there were two infarcts in the celecoxib group compared to one infarct in the NSAID group. Those rates are not different.

DR. HARRIS: Any other questions?

[No response.]

DR. HARRIS: Okay. We will take a break. It's 10:15, and we will be back in 15 minutes.

[Break.]

DR. HARRIS: We would like to resume and in this portion of our session, we are going to get a presentation from the FDA. We will start with Dr. Lawrence Goldkind.

FDA Presentation

GI

Lawrence Goldkind, M.D.

DR. GOLDKIND: My name is Dr. Goldkind. I will be reviewing some of the highlights of the gastrointestinal review of the CLASS study.

[Slide.]

First, I will briefly review some of the study

design highlights, which will overlap some with the presentation by Dr. Lefkowith. Then, I will review some of the results specifically the primary analysis as specified, which was complicated ulcer.

The term CSUGIE is only here, it will be reproduced a few times, but since the committee had received documents littered with that term, we wanted to make it clear. Complicated ulcer will be used in place of this term which, for the rest of the audience, stood for a clinically significant upper GI event, but they are identical for purposes of this discussion.

The initial intent-to-treat population, and then important subgroup analyses as have been discussed, aspirin and non-aspirin, important for obvious reasons.

Then, I will discuss the composite endpoint, the symptomatic ulcers combined with the complicated ulcers as was eloquently described by Dr. Geis, again, the intent-to-treat population and the subgroup analysis of aspirin users and separately non-aspirin users.

[Slide.]

I will briefly discuss high risk populations and make several concluding remarks.

[Slide.]

The original protocol stated that, "The null hypothesis being tested is that there is no difference in

the incidence of clinically significant upper GI events" between Celebrex and each of NSAID groups, ibuprofen and diclofenac.

[Slide.]

Some highlights from the original statistical plan stated that, "Two primary treatment comparisons will be performed: celecoxib vs. ibuprofen and celecoxib vs. diclofenac.

"A stepwise procedure will be used to strongly control type 1 error. In this procedure, the first step is to test the overall hypothesis whether celecoxib and the pooled NSAIDs are different.

[Slide.]

"If the test is not significant, the null hypothesis is retained and the procedure stops. If the test is significant, the second step will be the pairwise tests between celecoxib and each of the two NSAIDs."

So, it is clear that the intent was to compare celecoxib to each NSAID, but to avoid issues related to multiplicity and the need for statistical correction, a stepwise approach was employed.

I will try and go through these briefly.

[Slide.]

The endpoint definition, perforation, obstruction, and upper gastrointestinal bleeding. Through the vast

majority of this slide and the presentation by the sponsor, a traditional definition as defined by the sponsor has been employed which, as has been described, requires clear evidence of blood loss with evidence of gastroduodenal injury.

An alternate definition was used in addition for a separate analysis just to get a look at more severe or potentially imminently life-threatening bleeding that would require gastroduodenal injury be documented along with signs of an acute major bleed, which would include transfusion, orthostasis, or a significant drop in hemoglobin of 2 grams per deciliter.

[Slide.]

Again, using the traditional definition, this required gastroduodenal ulcer or erosion in addition to one of the following: hematemesis, active bleeding at the time of endoscopy, stigmata of recent bleed, which we saw some photos of earlier, and I will just make a point that in these cases, again, the quantitation of bleeding wasn't specified. Again, certainly these are very important endpoints, but this is where the differentiation with the more rigorous or severe bleeding definition, the alternate definition is relevant.

[Slide.]

Melena, hemoccult-positive stool, and fall in

hematocrit or hemoglobin. Hemoccult-positive stool and orthostasis or hemoccult-positive stool and the need for transfusion on clinical grounds.

[Slide.]

Again, to briefly go through the issues of dose selection. Again, obviously, the proof of hypothesis was important to test and to be sure that there wasn't simply a shallow dose dependency of any GI safety that may be demonstrated.

The dose creep phenomenon has been discussed by Dr. Witter. Particularly in chronic illnesses, particularly in painful conditions, a dose creep phenomena is anticipated, and this would be particularly true if there was a safety advantage suggested for a particular product, so that this was again part of the reason for building this high dose into the design.

Again, the margin of overall safety as opposed to organ-specific safety was important. Obviously, if the overall safety is not maintained at a higher dose, it is important to know, so that you can put any organ-specific safety information into a broader context.

Of course, the 8 mg a day dose is the 2X for rheumatoid arthritis, but it is the 1X for another chronic condition, familial adenomatous polyposis, and, of course, the future, we don't know.

[Slide.]

As the sponsor has pointed out, multiple aspects of the study address the issue of generalizability in terms of the population including both OA and RA, the fact that two comparators were included, and the fact that there were minimal exclusions, and as has been pointed out, significant renal or hepatic dysfunction, baseline occult GI bleeding, and in the absence of an exclusion of aspirin as has been discussed.

[Slide.]

In terms of the study duration, a quote from the original protocol states that, "The trial will continue until the anticipated number of clinically significant upper GI events have been observed in both studies. Minimum participation for an individual is 26 weeks and maximum study participation is 52 weeks."

[Slide.]

So, in summary, the study was well designed and included several important components. It addressed the issue of chronic exposure to assess chronic safety. High dose to assess the robustness of any safety claim. Multiple comparators in an attempt to address generalizability.

Rigorous and well-defined endpoints, and the large trial size allowed for comparative data on overall safety including uncommon toxicities.

[Slide.]

I will briefly review the results.

[Slide.]

These are the results from the primary endpoint, that being complicated ulcer in the entire population, and as the cumulative rates indicate, there was no meaningful difference between the three groups.

[Slide.]

Next, there will be a graph of the time to complicated ulcer, a survival analysis, again using the traditional definition for the entire population.

[Slide.]

The only point to make here is that events continued to accrue throughout the study period in the Celebrex group, which is highlighted here, while the diclofenac group experienced only one event beyond the three-month period, and the ibuprofen group accrued no further events after approximately a half a year.

[Slide.]

In terms of the subanalyses for the complicated ulcer endpoint, non-aspirin and aspirin users.

[Slide.]

For the non-aspirin users, the results are shown here, and there was no statistically significant difference between diclofenac and Celebrex. There was a numeric

difference between ibuprofen and Celebrex. This is an uncorrected p-value, and it is put here to give a sense of magnitude of difference, however, it doesn't have the same statistical rigor as a prespecified endpoint since multiple comparisons were made before getting to this comparison.

[Slide.]

Again, the survival curve for the complicated ulcer in non-aspirin users.

[Slide.]

A similar pattern although obviously, fewer events through the study period, but again, events were early in the NSAID comparators, and the majority were early in the Celebrex group, as well, however, events did continue to accrue throughout the course of the study.

[Slide.]

For the aspirin users, the cumulative rates are displayed here. There is no statistical difference between the groups. There was a paradoxical finding in the ibuprofen group in that the rate was, in fact, lower than the other traditional NSAID comparator in Celebrex.

It is important to note that while a denominator of 412 is large for an efficacy study for an analgesic, for a large outcome study, this is not a large sample size and only one event in that sample size, so this may be hypothesis generating, but it should be looked at in the

context.

[Slide.]

Summarize the findings for complicated ulcers. For the primary analysis, no differences between Celebrex and NSAIDs combined or individually was demonstrated.

For non-aspirin users, there was a strong trend favoring Celebrex compared to ibuprofen, however, no difference was shown between Celebrex and diclofenac.

Finally, in the analysis of aspirin users, no differences between Celebrex and diclofenac were shown. There was a paradoxical trend favoring ibuprofen compared to both Celebrex and diclofenac, but once again, important caveats relate to the sample size, the fact that the study was not stratified for aspirin use, so there may be differences that we don't see in these results.

[Slide.]

Now, to discuss other relevant analyses specifically the composite endpoint of symptomatic complicated ulcers, just to point out in the original protocol, it states that, "Symptomatic upper GI ulcers, documented by endoscopy or upper GI barium x-ray with no evidence of perforation, bleeding or obstruction will be categorized and summarized separately."

So, the composite endpoint was not a prespecified endpoint.

[Slide.]

It is, as has been discussed, an important and certainly clinically relevant endpoint, and the ascertainment of these events was prespecified.

[Slide.]

For the entire population for this endpoint, the results are shown here. There was no meaningful difference between the diclofenac and Celebrex group with a very strong trend in favor of Celebrex compared to ibuprofen. Once again, this is a nominal p-value for an analysis that was not prespecified.

[Slide.]

Now, we will look at the survival curve, that endpoint, and this is somewhat different than the pattern that was seen for the primary analysis of complicated ulcers in that all three groups continued to accrue events going far out into the study.

[Slide.]

For the non-aspirin users, again, the cumulative rate. There was no meaningful difference between the Celebrex and the diclofenac group, where again there was a strong trend--this is the nominal p-value--for the ibuprofen group compared to the Celebrex group.

[Slide.]

The time to endpoint survival curve for the non-

aspirin users is displayed here, and the diclofenac and Celebrex groups virtually overlap, but they clearly separate out from the ibuprofen group shown here.

[Slide.]

Now, for the aspirin users, although the rates are higher in all groups compared to non-aspirin users or the entire cohort, the flip pattern between ibuprofen and the other comparators is seen similar to what was seen in the primary analysis of complicated ulcers. There is no statistically significant difference between the groups here, but nominally, the ibuprofen group, rather than being higher, is actually slightly lower here.

[Slide.]

Conclusions of this analysis of the composite endpoint. There was prespecified ascertainment of data, but the endpoint was not prespecified. As mentioned, it is clearly a clinically relevant endpoint.

There was a strong trend in favor of Celebrex compared to ibuprofen in the non-aspirin users with no difference demonstrated between Celebrex and diclofenac in the non-aspirin users.

[Slide.]

In aspirin users there was a paradoxical trend favoring ibuprofen compared to both Celebrex and diclofenac similar to the pattern that was seen at the primary endpoint

of complicated ulcers.

[Slide.]

Now, briefly, I will show one slide using this alternate definition, which was a prespecified definition, although not the primary analysis. Again, sign of GI bleeding be it hematemesis, melena or hemoccult-positive stool n the face of gastroduodenal ulcer erosion was required plus signs of a major bleed, which would include either a greater than 2 gram drop in hemoglobin once hydration after an acute event had taken place, or if transfusion was required acutely before equilibration of final hemoglobin less than or equal to the pre-bleed level, or orthostatic hypotension or a supine blood pressure of under 90/60.

[Slide.]

So, as you can see, this is a much smaller set that are likely to meet this definition, and there was no statistically significant difference seen between the groups at this endpoint.

[Slide.]

In terms of the high risk populations, as has been discussed earlier, age greater than 75, history of upper GI bleed, and aspirin use were all associated with a substantially higher relative risk compared to those that were not in each of these categories. This is univariate

here. The relative risk extends across both comparators.

[Slide.]

For the composite endpoint, symptomatic and complicated ulcers, the same general trend is seen with a substantially higher relative risk for those that meet each of these criteria compared to those that don't.

[Slide.]

Now, when considering high risk populations, you have to take into account an associated risk that is related to the underlying risk factor versus an attributable risk associated with the therapy.

If age and history of ulcer complications are independent risk factors separate from NSAID use for ulcer disease, then, the findings of high risk in association with the therapy may represent the intrinsic underlying risk rather than a drug effect or causality.

On the other hand, it is possible that there is an interaction between the underlying risk factor and the drug related risk, such that an exaggerated or a higher risk that is, in fact, attributable to therapy would need to be considered, in which case there would be causality.

[Slide.]

The overall conclusions. No statistically significant differences were shown for the entire population for the primary endpoint of complicated ulcer between

Celebrex and the NSAID comparators combined or individually.

An important relevant endpoint of the composite of symptomatic and complicated ulcers suggested a difference between Celebrex and ibuprofen in favor of Celebrex. No difference was seen between Celebrex and diclofenac.

[Slide.]

Hypothesis-generating findings include the fact that co-administration of aspirin was associated with an increased and similar risk of complicated ulcers in both Celebrex and diclofenac group in the range of 4-fold.

The same trend was seen at both the primary analysis and the composite endpoint analysis.

[Slide.]

The ibuprofen group that required low dose aspirin experienced a lower rate of complicated ulcers than either of the other two groups. Again, this trend was consistent between the two analyses.

[Slide.]

It is unclear whether these paradoxical findings associated with the concomitant use of aspirin and ibuprofen simply represent random findings or whether they represent a true differential interaction between aspirin and NSAIDs in terms of the upper GI toxicity.

[Slide.]

Further study is needed to clarify the safety of

co-administration of aspirin and NSAIDs COX-2 selective agents.

No conclusions regarding the safety of Celebrex compared to traditional less selective COX inhibitors as a group are possible.

Thank you.

DR. HARRIS: We will next hear from Dr. Witter.

Medical

James P. Witter, MD., Ph.D.

DR. WITTER: Let me first start by saying I am glad to know that others beside the agency utilize acronyms.

[Slide.]

As you know, CLASS stands for Celecoxib Long-term Arthritis Safety Study. By agreement, what I will be discussing is the entire database. Should you see any asterisks on any of the numbers, it indicates a level at a p .05, less than .05, and what I am going to try and do is summarize the data rather than try and regurgitate it, and get into a bit more discussion of the aspirin subgroups, so we will see if I am successful.

[Slide.]

Again, just to reiterate some of the basic of the CLASS protocol is that it was a combination of two protocols, Study 035, which has its NSAID comparator ibuprofen, and Study 102, which had diclofenac as its NSAID

comparator.

Celecoxib, as we now know, was used at the 2x dose, which as it turns out is the 1x dose for FAP.

It was a large study conducted in 386 sites throughout the U.S. and Canada involving, as we now know, almost 8,000 patients.

[Slide.]

The inclusion criteria--and I think we need to redefine when we say large and simple trials, we have to come up with something else because I think we appreciate that these are very complex results that we have gotten here, and the intent was, as you have heard several times, to make this as a real world as possible, and I am sure some of the discussion will center around whether that was successful or not--but really, the inclusion criteria included those who were old enough to give written informed consent.

You have to have OA or RA for about three months duration, and you then you needed to have an NSAID type compound, and that you were not pregnant.

The exclusion criteria were also similarly simple although they excluded folks with GI disease or ulceration actively or that had significant renal hepatic disease or coagulation defect and active malignancy, but again, how this represents the real world might be a point of

discussion later.

[Slide.]

The baseline demographics, whether you like to look at means or medians, was approximately 60 years in terms of age, there were about 11 percent of the patients that were 75 years or older.

This study was conducted primarily in white females. Approximately 27 percent of patients had RA, 10 percent of patients had a history of either GI bleed or gastroduodenal ulcer, and about 21 percent were taking aspirin for cardiovascular prophylaxis.

[Slide.]

Again, just to reiterate, the use of concomitant medications, things like NSAIDs, either Rx or OTC were prohibited, but as we heard, there were a substantial number of patients who did use these things primarily for things like headaches and other reasons in the short term. If it was long term, they were excluded. Prohibited also were anti-ulcer drugs and antibiotics as they might be utilized to treat for H. pylori.

Allowed were, as we now know, aspirin, antacids for treatment for prophylaxis for osteoporosis, things like methotrexate and corticosteroids for the patients with RA, and then algesics ranging from Tylenol to oxycodone on an as-needed basis, again with the idea to keep folks in the

trial.

[Slide.]

Just a bit about aspirin use in the CLASS trial. It was, as we know, at 325 or less mg on a daily basis, and again it was for those who were at risk for certain events. However, as Dr. Goldkind indicated, it was not stratified in the CLASS study. Therefore, the dose and duration may have varied in the study with regard to this endpoint.

I think probably the safest thing to say is that no conclusions regarding aspirin co-use can be drawn from the CLASS study, but some interesting observations and potentially possible directions for future studies, which again may be part of our discussion this afternoon.

[Slide.]

Statistical issues, just to summarize, was the null hypothesis, that celecoxib was, in fact, equal to NSAIDs for the primary outcome of complicated ulcers.

It was estimated that there were going to be 40 events, 8 in the roughly 4,000 celecoxib patients, 32 in the roughly 4,000 NSAID patients. It was assuming a withdrawal rate of 35 percent, power to 90 percent, and there was significance at 0.05 on two-sided testing.

[Slide.]

Now, again, what I am trying to do is simplify the data. I don't want to get into a line listing kind of

approach because we have seen lots of data, and I don't have any substantial differences from the sponsor on their numbers.

So, of the folks that are in the ITT population, we can see here that more people tended to complete the study in the diclofenac group, whereas, more tended to be withdrawn in the ibuprofen group.

What is not up here are the reasons, and I think we discussed that a bit earlier. For ibuprofen, there was more that left the trial for treatment failure of noncompliance, whereas, in the diclofenac group there were more that left because of adverse events. Interestingly and refreshingly, there were no patients lost to follow up, which is something we seem to be discussing a lot at these venues.

[Slide.]

Now, admittedly, efficacy in the CLASS trial was not an endpoint, but I think it is worthwhile just spending a little time to review this. If one looks at patient globals, patient assessment of pain on the VAS scale, the disability indices of health assessment questionnaire or the generic SF-36 or patient withdrawal rates, if those are measures of efficacy, then, what we can say is that celecoxib as utilized in the CLASS trial was not shown to be more effective than NSAIDs.

However, there was an interesting trend if you compared against the original database of less patients being withdrawn in the CLASS trial than the NDA, suggesting that there may, in fact, be some utility to a higher dose for a time period.

[Slide.]

Now, I am not going to go through all the GI summary, all the data, I am just going to try and summarize it, and again to reiterate that the primary endpoint was that of complicated ulcers in contrast to symptomatic ulcers, and there were 38 of these events which are uncensored. This was looking at all the three groups.

Celecoxib was not statistically significantly different than either of the individual NSAIDs or pooled NSAIDs, so therefore, celecoxib did not meet the primary endpoint of this trial, and there is no disagreement on that.

[Slide.]

However, when you look at the primary endpoint in a more restrictive fashion, and in particular what I am referring to here is those folks who were not taking aspirin, there were a total of 22 uncensored events in all the groups, and in this case, celecoxib was different with a nominal p-value of 0.03, and as Dr. Goldkind had indicated, this was not corrected for multiplicity, nor was this a

prespecified endpoint, but it was different than ibuprofen, but not diclofenac.

[Slide.]

When the endpoints were expanded to include, as we now know, complicated and symptomatic ulcers, there were 105 events in all groups, and here again celecoxib was able to show that it was better than ibuprofen, but not diclofenac.

When we take that expanded population of complicated and symptomatic ulcers, and then look at only the aspirin non-users, there were 59 events, uncensored events in all the group, and once more, celecoxib did show that it was better than ibuprofen, but not diclofenac.

So, a consistent finding here is that under no circumstances of patient group, length of trial, was there any difference between celecoxib and diclofenac.

[Slide.]

Again, I am trying to get a little different spin to the data here rather than just repeat what we have seen.

So, looking at GI adverse events and looking at all patients, those that did take aspirin, those that didn't take aspirin, it can be seen here that whether we look at the data in terms of any adverse events, or any of those adverse events leading to withdrawals, and it doesn't matter what patient population we look in, whether it is all patients in the aspirin users or in the non-aspirin users,

there were more of these events in the diclofenac group.

Also, it certainly seems to point out the effects of aspirin as you look across and compare aspirin to non-aspirin, the event rate is higher in the aspirin users across the board.

[Slide.]

Now, looking at all adverse events and going back to what we just saw with the GI slide, we can see here that looking at any adverse event or severe adverse events, or adverse events that led to withdrawal, once again, the highest incident rates were in the diclofenac group.

However, when you look at the serious adverse events, there was a higher rate in the celecoxib group, and if you are wondering about the differences in numbers, these are as percentage, the sponsor presented it as patient year data before.

[Slide.]

Deaths, it certainly could be argued one of the most serious adverse events there is in a trial, there were 36 all-cause deaths in this trial. There were 19 in the celecoxib group, which comes out to be 0.5 percent, 9 in the diclofenac group, which is 0.5 percent, and 8 in the ibuprofen group, which comes out to be 0.4 percent.

Most of these deaths were in patients age 65 years or older, and most of these were cardiovascular in nature.

That came out to be 58 percent in the celecoxib group, 56 percent in the diclofenac group, and 63 percent in the ibuprofen group.

[Slide.]

Looking at this data in a slightly different way, on patient years and breaking it up into aspirin users and non-users once more, whether we look at all-cause mortality, whether we look at cardiovascular mortality, whether we look at it in aspirin users or non-aspirin users, celecoxib is no worse than any of the other comparators.

[Slide.]

Turning to renal adverse events--and again my attempt here is to simplify the data--whether you look at any event or any of those events that led to withdrawal, there was a higher incidence of these events in the ibuprofen subgroup.

If you look at the data, which we have asked the sponsors to do, in a contingency type approach, for example, where you have increases of BUN and/or creatinine above the level specified here, we see that there are more of these types of events in the diclofenac group.

[Slide.]

Looking at cardiovascular events, and in this particular slide, again for simplicity, I have combined the categories into edema, which, for example, represent the

line listings of edema, peripheral edema or generalized edema, anginal disorders, and thrombophlebitis, again, these are combination, it is more of a mixed picture.

You can see, for example, that in terms of edema, there tends to be more events in the ibuprofen group, whereas, with anginal disorders, there tends to be more in the ibuprofen group, it doesn't whether aspirin or not, and in looking at thrombophlebitis and the events in that category, again, it is a mixed picture, in aspirin users more in diclofenac, non-aspirin users, more so in the non-aspirin users.

[Slide.]

Looking at serious cardiovascular events--and again I have combined categories here, somewhat similar to the last one although there is atrial added in here--and this time just focusing in on the non-aspirin population, there appear to be slightly more events in the atrial, anginal, and MI categories for celecoxib as compared to the other groups. However, this is not the case for the combined thrombophlebitis type events.

The aspirin data, I don't have it here, but it is a mixed picture, and in none of the categories is celecoxib leading or have the highest incident rates compared to the others.

[Slide.]

Turning to hepatic adverse events, if you look again at any adverse event or any adverse event leading to withdrawal, we once again see that diclofenac has the highest rate, and what I have done here is again looking at a contingency type of approach, and looking at multiples above the upper limit of normal, so, for example, the liver enzymes AST or ALT combined or combining one of those enzymes with alkaline phosphatase or total bilirubin or doing those alkaline phosphatase and bilirubin together, once again we see that there are more events in the diclofenac group, and I think this data nicely suggests that whatever the problem is, it is in the liver.

[Slide.]

Looking at adverse events that impact the skin, whether you are discussing it in terms of rash or pruritus, looking at the overall events or those events that led to withdrawal, there were more of these events in the celecoxib group. However, for the most part, these were not severe reactions.

[Slide.]

Now, just trying to summarize a little bit of the aspirin data--and again I think we are only looking at these just as some observations, but interesting nonetheless--as Dr. Goldkind had indicated, whether you look at the complicated ulcers, and actually I should have had up here

symptomatic ulcers, as well, we saw that aspirin co-use with celecoxib and diclofenac led to an increase in these events, but there seemed to be a paradoxical, which is the term that we are using, decrease or lessening of events with ibuprofen.

However, when you look at GI adverse events or withdrawals because of an adverse event, consistently across the board you see that co-use of aspirin increased the events in all three groups.

[Slide.]

When you look at cardiovascular events, we have what I will call here a mixed picture. In terms of overall mortality, we see that it increases with celecoxib and diclofenac, but it appears to go down with diclofenac.

In terms of MI, it goes up in all three groups, but if you look at thrombophlebitis, it goes up in diclofenac and ibuprofen, but it appears to go down in the celecoxib groups. So, aspirin, as I say, has some interesting, but not necessarily consistent results.

[Slide.]

So, overall safety in terms of the GI tract, once more, celecoxib was unable to demonstrate a statistical superiority to either ibuprofen or diclofenac when considering the primary endpoint of the CLASS trial.

However, celecoxib was able to demonstrate a trend

in superiority to ibuprofen (only) in patients not taking aspirin and with broader endpoints meaning particularly complicated and symptomatic ulcers.

[Slide.]

In terms of renal safety, celecoxib does not effect acid-base balance more than diclofenac or ibuprofen. I should note that this is a fulfillment of a Phase IV commitment by the sponsor.

There does not appear to be any large effect on renal adverse events relative to ibuprofen or diclofenac.

Although it is not seen in the CLASS trial, serious renal disease, such as acute renal failure or interstitial nephritis, are in the current labeling for Celebrex.

[Slide.]

In terms of cardiovascular in the CLASS trial, there was no apparent adverse effect on cardiovascular mortality or serious adverse events related to thrombosis relative to ibuprofen or diclofenac, although this does not exclude that there is some kind of a lesser cardiovascular effect as I think we have heard this morning.

However, events such as myocardial infarction, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebral vascular accident, vasculitis and other events are in the current label for Celebrex.

[Slide.]

Hepatobiliary safety. Adverse events are not more frequent than seen with ibuprofen or diclofenac, and although not seen in the CLASS trial, such events as hepatitis, jaundice, and liver failure are in the label.

[Slide.]

In terms of skin, rash and pruritus, as I pointed out earlier, are generally mild to moderate, are important adverse events that frequently lead to withdrawal with this compound. Once again, serious adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme, again, they are in the label.

[Slide.]

Overall safety in terms of deaths, there were no deaths from hepatobiliary, renal, dermatologic, or GI causes. The latter, I find particularly interesting.

Deaths from the cardiovascular causes appear to reflect more the population studied rather than any new adverse effect of celecoxib, and the deaths from cardiovascular causes are not more common in the celecoxib group as compared to the controls.

[Slide.]

Trying to make a grand summary, then, of the overall safety of celecoxib, in this case what I am going to do is look all the way from the NDA and through to the

current data, it appears that celecoxib looks more like an NSAID than placebo.

[Slide.]

Finally, as I had discussed earlier, and we still I think tend to want to do this, make comparisons against NSAIDs and COX-2's, particularly in regards to safety, so I am wondering here what is the best way to look at the data. For example, is beating one NSAID the same as beating them all? On the other hand, is losing to one NSAID the same as losing to them all?

Thank you very much.

DR. HARRIS: Thank you, Dr. Witter.

Are there any comments, questions related to clarification from the committee? Yes, Dr. Sampson.

DR. SAMPSON: Dr. Witter, I was wondering if you could just say a few more words about what you call the null hypothesis of Celebrex being equal to "NSAIDs"? At least when I read the material, it looks to me like there is two null hypotheses as opposed to some sort of a composite, and the two null hypotheses are Celebrex versus ibuprofen, and Celebrex versus diclofenac.

Are I misunderstanding that is some sense?

DR. WITTER: I think the first go-around was to look at the combined NSAID groups and then to look at the individual compounds to preserve the type 1 error.

DR. SAMPSON: At least my reading of the statistical issues, the overall test was just an artifice to protect the other conclusions, it was never really intended as a scientific null hypothesis at least from my understanding of it. Maybe I need to be corrected on that.

DR. GOLDKIND: I think that that is true. It was a stepwise approach, but the primary hypothesis was related to step 2 rather than step 1, and statistically, if the first step failed, one would not go beyond that, and so in a simple sense, one would not have gone beyond that first null hypothesis of the group comparisons for that endpoint.

DR. SAMPSON: And if the first step were a success, one wouldn't then conclude that you were superior, quote, "to NSAIDs."

DR. GOLDKIND: The spirit of the study was to look to see how generalizable it is, so looking at the individual NSAIDs was the intent.

DR. HARRIS: Yes, Dr. Wofsy.

DR. WOFSY: I think I have a similar question in regard to your last comment. I wonder if you could amplify on, you said celecoxib looks more like an NSAID than like placebo, but there is no placebo in these data.

How do you come to that conclusion? Maybe to broaden the question, if the issue in this study was to look at whether or not the GI labeling was necessary, that is, is

there a GI risk compared to placebo, how do we address this question in a study that has no placebo?

DR. WITTER: The slide had in there that was including the discussion of the NDA material, in which case there were a lot of placebo controls, and I was trying to go back to the original presentation where were always looking at how these compounds compared, not only against NSAIDs, but also against placebo.

We had a substantial discussion, for example, in terms of GI events, whether these rates would look like placebo, so that comment was meant to kind of be a broad sweeping compilation of all the data from the NDA up and including the CLASS trial and looking at all the safety parameters, be they GI events, renal events, as I discussed, because that has always been kind of an issue is the overall safety profile of these compounds, what is the best way to view them.

DR. HARRIS: Any other comments? Yes.

DR. SAMPSON: One further clarification. In patients not taking aspirin, it was indicated that there was a trend, and the p-value is 0.03 of Celebrex versus ibuprofen, and just for my own clarification, I understand this wasn't a preplanned analysis and thus would not necessarily be subject to the multiple comparison procedures, however, if one were to use the multiple